

The NIH Role in Fostering the Nation's Leadership in Biotechnology

Proceedings of the 51st Meeting
of the
Advisory Committee to the Director
National Institutes of Health

June 24-25, 1985



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NATION'S LEADERSHIP IN BIOTECHNOLOGY

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FOREWORD

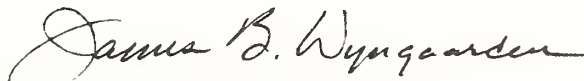
The emergence of biotechnology, which has occurred largely as a result of the sustained support for basic research in molecular biology and immunology provided by the NIH over the past several decades, has created an unprecedented set of issues, concerns, and opportunities. The manner in which these challenges are addressed could determine to a large extent the future industrial competitiveness of the U.S. biotechnology industry.

This report of the proceedings of the 51st meeting of the Advisory Committee to the Director, NIH (DAC), on the topic of "The NIH Role in Fostering the Nation's Leadership in Biotechnology" represents the results of two days of intense deliberation on topics covering: (1) the history and development of biotechnology and its future prospects; (2) the elements of a science policy for biotechnology; (3) the role of NIH in the support of training for biotechnology; (4) issues in risk assessment and risk management associated with biotechnology; (5) the manpower, financial, regulatory, and informational barriers to industrial competitiveness; and (6) the appropriate role of NIH in fostering biotechnology.

For this meeting, the regular membership of the DAC was augmented by the participation of invited representatives of large and small biotechnology firms, pharmaceutical companies, instrument companies, universities, Federal departments and agencies, and private foundations.

This meeting formed a vital part of an ongoing process through which the NIH is attempting to determine the most appropriate role it might play in contributing to the growth and development of the U.S. biotechnology industry. In view of the importance of the topic and the timeliness of the meeting, we wish to share with you the views, opinions, and suggestions that have been offered for consideration concerning future activities of the NIH in support of biotechnology.

The suggestions made at this meeting are being examined by the NIH in an effort to sort among the myriad of emerging needs and to identify activities which represent a logical and natural extension of current NIH capabilities. We look forward to continued contributions from all relevant communities as we proceed with this important task.



James B. Wyngaarden, M.D.
Director
National Institutes of Health

EXECUTIVE SUMMARY

The 51st meeting of the Director's Advisory Committee was held on June 24-25, 1985, to discuss the role of NIH in support of the new biotechnology. This summary is not intended to convey the full range of views and opinions expressed during these deliberations but, instead, is offered to denote the general thrust of these discussions. A detailed account is provided in the body of this report.

Dr. James B. Wyngaarden, Director, NIH, opened the meeting with a working definition of biotechnology and an overview of some of its potential applications in the areas of health care, animal and plant agriculture, and pollution control. He noted that many major technological advances are accompanied by new issues, concerns, and challenges, and that biotechnology is no exception. For example, there has been much public debate over hazards presented to the public and to the environment by the products and the production processes. Ethical concerns are aroused by the nascent capability to alter human genetic material. Another issue is the potential for conflict of interest evolving from the new relationships forged between industry and academia. A balance must be struck between the interests of the biotechnology industry in maintaining a competitive edge in the world market and the need for teaching institutions to adhere to their commitment to train the next generation of scientists, many of whom will contribute to the knowledge base and manpower pool that supports the private sector.

Dr. Wyngaarden reviewed the extent of NIH's commitment to biotechnology, both through its extramural grant program and through research and research training conducted in the intramural program. He related past events that had prompted self-examination of the NIH mission and occasions when the mission had been extended in selected areas to meet specialized needs. However, the traditional responsibility to concentrate our efforts and resources on the support and conduct of fundamental biomedical research remains intact. This sustained investment in basic research underlies all of the science and methodology employed in modern biotechnology.

Historical Development and Future Prospects of Biotechnology

The first panel cited some of the achievements that led to the development of modern techniques that are essential to biotechnology. For example, one speaker traced the experiments that preceded chromosome mapping and the actions of restriction enzymes, both of which are harnessed to excise and recombine pieces of DNA. Another described the state-of-the-art of molecular genetics, noting that it is now possible to clone virtually any gene or DNA segment from any organism. Investigations of the regulation of gene expression in eukaryotes and prokaryotes yield much important fundamental information regarding evolutionary processes and also have obvious commercial implications. Future uses of biotechnology, such as the application of

molecular genetics to the diagnosis and treatment of inherited diseases, were described in conjunction with the caveat that gene therapy research is still at an early phase. Parallel techniques are also being used to study the expression and carcinogenicity of oncogenes. The imagination of the public has been caught by the experiments involving insertion of a gene for growth hormone resulting in a larger-than-average mouse; however, the potential for other kinds of genetic manipulation raises ethical and moral questions. In the opinion of one expert, human gene therapy at the germ cell level is not yet on the horizon.

Participants emphasized the necessity for thorough training in the fundamental aspects of biology and chemistry as prerequisites for careers in research, a capacity they see diminishing over time. A disturbing consequence is that students develop technical skills without sufficient background to enable them to apply these skills to fundamental questions.

Federal Science Policy for Biotechnology

The next session was devoted to the examination of a national policy for biotechnology and the NIH role within this context. The chairman reviewed current Federal activities related to science policy in general and some dealing with biotechnology specifically. The White House Office of Science and Technology Policy (OSTP) is leading an effort to develop a coordinated system for regulating various aspects of research and commercial uses of biotechnology.

An OSTP representative suggested that the DAC address how government can develop talent and stimulate a national sense of teamwork in biotechnology by overcoming an adversarial relationship that has sprung up among government, academia, and industry. NIH achievements in creating a knowledge base that undergirds advances in disciplines beyond medicine were applauded, and NIH was encouraged to continue a research program that leads to better health care while providing training that will enable new talent to capture the fruits of the biological revolution. Included in this role was the suggestion of an increasing responsibility in developing the knowledge and techniques necessary for advancing biotechnology and facilitating the merging of the biological sciences with other scientific disciplines.

An industry representative echoing earlier speakers expressed the opinion that "we should let NIH be NIH"; that is, the best protection against losing our competitive edge in biotechnology is to continue to focus on basic research and to secure the best people and the best ideas. In his view, it is the responsibility of the private sector to develop commercially viable products from the pool of available knowledge.

Discussion following this panel centered around the direct relationship between NIH's broad-based support for fundamental research and progress in biotechnology that might be disrupted by a form of micromanagement that restricts cross-fertilization between fields. The notion that NIH should initiate a program in product development garnered no support among meeting participants.

NIH and the Support of Research Training in Biotechnology

There was a consensus that increased research training in the areas of molecular genetics, biology, immunology, and virology is essential to maintaining a lead in biotechnology and overcoming a personnel shortage that already exists. Another mechanism for addressing the growing shortage of skilled personnel is to retrain the current work force so that they may keep pace with the latest advances in these disciplines.

Biotechnology, Risk Assessment, and Risk Management

The focus of the next panel was Federal regulation of biotechnology. The FDA Commissioner described his agency's policies for overseeing the safety of products developed using biotechnology as similar to those generated with classic techniques; however, a core of special experts are needed to assess risks specific to biotechnology. Regulatory agency representatives agreed that existing legislative authority is sufficient to deal with such issues and that these cases are best dealt with on a case-by-case basis. The need for coordination among agencies with responsibility for regulating the products of biotechnology was stressed. Concern was voiced that more research is necessary to support regulatory efforts.

Barriers to Industrial Progress (Manpower, Financial, Regulatory, Information Access)

A major portion of the meeting was devoted to an examination of current and potential barriers to industrial progress, including manpower, financial, regulatory and information access. Representatives of the private sector were asked to enumerate the factors necessary to maintain a competitive position in the world biotechnology market. While some of the suggestions fell outside the purview of NIH, all agreed that replenishing the pool of trained personnel is crucial, as is continued advancement of basic understanding of life processes.

The supply of scientists who possess general knowledge in the areas of molecular biology, molecular genetics, chemistry, virology, immunology, and biophysics is being rapidly outstripped by the needs of industry and academe. Without competent teachers in the universities, there will be no one to prepare a new generation of researchers to produce further advances in the basic sciences as well as in biotechnology.

Proposals related to research training included: increased collaboration between government, industry, and academia (enhanced by a multidirectional flow of researchers), encouraging U.S. postdoctoral fellows to seek further training in selected laboratories abroad, and greater emphasis on interdisciplinary training. Several participants asserted that NIH training programs ought to include education in bioprocess engineering and fermentation sciences, citing the MIT Biotechnology Process Engineering Center as a model.

A recurrent question centered on defining the appropriate limits of federally sponsored basic research versus applied research that traditionally falls in the domain of the private sector. Varying views were expressed concerning the appropriate division of responsibility for funding projects in the gray area between product-oriented research and fundamental investigation, labeled "generic applied research." Some participants felt that NIH support for research aimed at improving bioprocessing or scale-up technology, or using plants as model systems, might be acceptable, assuming that the knowledge obtained would be broadly applicable. It was noted that such research is already conducted under NIH auspices and that the results are as readily employed in answering fundamental questions as they are in commercial applications.

Several speakers addressed the stimulatory effects of changes in Federal regulations with respect to tax incentives and patent policies but noted that the NIH influence in these arenas is negligible. However, the NIH can exert considerable force in terms of "people exchanges." For example, allowing NIH intramural scientists to consult for industry or opening Federal laboratories to industry researchers will promote important transfer of ideas and techniques. A program for data base and software exchange was also proposed. It was suggested that these initiatives and others that stimulate information-sharing between government and industry scientists might also reduce redundancy of effort.

NIH's Role in Fostering Biotechnology

Summary remarks tended to bolster the view that NIH should continue on its present course of support for basic biomedical research and research training. The concept that this policy has earned for the U.S. the preeminent position in the world in biotechnology was reiterated repeatedly. However, an important facet of this obligation is the maintenance of the research infrastructure. One speaker noted the deleterious impact of the demise of the Health Research Facilities Act and encouraged NIH to respond to the facility needs of its constituency. Other comments dealt with industry needs for trained personnel and for expanding the scope of investigation into problems that apply to commercial scale-up. These issues will form the basis for continued discussion and examination of the areas where NIH boundaries might be made more flexible to contribute to increased industrial competitiveness while continuing to advance our fundamental understanding of the life processes.

ADVISORY COMMITTEE TO THE DIRECTOR, NIH
Minutes of the 51st Meeting

June 24-25, 1985

The 51st meeting of the Director's Advisory Committee (DAC) was held on June 24-25, 1985, at the National Institutes of Health, Bethesda, Maryland. Dr. James B. Wyngaarden, Director, chaired. (See attachment for lists of members and participants.)

OPENING REMARKS

Dr. Wyngaarden opened the meeting by stressing the fact that the topic of biotechnology is of intense interest both in academia and industry and that NIH has a special interest in the future of the biotechnology industry, since this industry is a direct result of the support provided by NIH over the past several decades to basic research in molecular biology.

Dr. Wyngaarden defined biotechnology as any technique that uses living organisms (or parts of organisms) to make or modify products, or to improve plants or animals for beneficial use. While this definition includes many traditional biological processing techniques--such as those used in making bread, cheese, and alcoholic beverages--there has emerged, largely within the last decade, a "new" biotechnology which comprises a collection of powerful techniques that can be applied to develop new products of commercial value.

Dr. Wyngaarden remarked that while few products of the new biotechnology industry have reached the marketplace to date, it is estimated that future sales of biotechnology products will be substantial.

As is true of many major advances, the emergence of biotechnology has also created a new set of issues, such as its effect on public health and the environment and its potential use to develop biological weapons. Further, biotechnology has raised questions for universities regarding their new relationships with industry. Other emerging issues deal with the national need to develop policies and programs to foster the growth of this new industry, given the increasingly competitive international marketplace.

Dr. Wyngaarden cautioned that while the U.S. currently enjoys a global lead in this area, we must guard against complacency by examining our current efforts in order to determine whether the total research and training needs of biotechnology are being met. Further, we must ask whether the general climate for innovation will continue to be conducive to progress in biotechnology.

Although our current levels of support for research related to biotechnology seem substantial, it has been suggested that a critical need exists for increased emphasis on generic research of the type that falls between the basic research generally supported by NIH and the proprietary activities undertaken by industry in the development of specific products. We must also determine whether increased training of personnel in certain selected areas of biotechnology is needed. Dr. Wyngaarden concluded his opening remarks by reviewing some of the current training initiatives under way in this area.

History of NIH Mission and Special Circumstances
Suggesting Reexamination

Dr. James B. Wyngaarden
Director, National Institutes of Health

Dr. Wyngaarden began the discussion by reviewing some of the events and forces that shaped the mission of NIH which occurred in the period beginning around the end of World War II. Wartime experience had demonstrated that Government and academia could collaborate in an extremely productive fashion, and the Bush Report of 1945 encouraged this partnership to continue. He mentioned that NIH will celebrate its 100th anniversary in 1987, and that the institution was small and directed inwardly for most of that century.

Efforts during those early years, Dr. Wyngaarden stated, were greatly aided by the enactment in 1944 of Section 301 of the Public Health Service Act, which provided a broad authority to conduct research. It was recognized that there were gross inadequacies in the existing base of biomedical knowledge and a severe lack of human and material resources necessary for the conduct of research. NIH chose to interpret this authority in its broadest sense by developing a long-range strategy to create a strong base of science which would later permit a more direct assault on specific health problems.

NIH began a strategy which involved the support of basic biomedical research at universities and the strengthening of those university departments in which the research would be conducted. Dr. Wyngaarden explained that this was principally achieved by training future investigators and supporting biomedical research through investigator-initiated research project grants awarded on the basis of scientific merit.

He related that those decisions proved to be farsighted and have resulted in the development of a vast network of scientists and research institutions which comprise an outstanding biomedical research enterprise. These principles have shown themselves to be enduring and remain as basic elements in NIH efforts to expand our current base of knowledge.

During the 1960's, continuing progress in biomedical research raised expectations for substantial improvements in medical care. This concern was, in part, reflected in the enactment of a broad range of new health legislation designed to improve the quality and availability of health care in the Nation.

Dr. Wyngaarden provided a number of examples of such Acts and summarized their intent by saying that this legislation provided discrete program recognition and specific expanded responsibilities for the application of existing knowledge through control and demonstration programs and public education.

As national goals and priorities broadened, NIH has periodically reexamined its mission and functions to determine whether opportunities exist to lend its particular strengths to emerging needs. For example, during the 1970's a strong sentiment arose for an increased Federal role in improving health care through the accelerated application of research results. Dr. Wyngaarden noted that in response to this growing concern, NIH in 1977 examined its existing technology transfer activities with the aim of identifying ways in which these efforts could be strengthened. As a result of this appraisal, there was established within NIH the Office of Medical Applications of Research (OMAR) to serve as the focal point for technology assessment and transfer activities.

A key element in this process is "consensus development," which brings together biomedical research scientists, practicing physicians, consumers, and others in an effort to reach agreement on whether a given medical device, drug, or procedure has potential medical value. This information is then disseminated through reports written by expert and lay members of Consensus Development Conference Panels.

Dr. Wyngaarden went on to say that OMAR also coordinates NIH medical and scientific reviews of issues related to Medicare reimbursement and submits the expert opinions to the Health Care Financing Administration. In addition, OMAR administers the NIH patent program, which promotes the transfer and commercialization of NIH-funded inventions.

Dr. Wyngaarden then provided another example of NIH extending its traditional role. During the late 1970's, it became apparent that concern had been growing over the increasing numbers of new chemicals being introduced into the environment and the threat of human disease posed by exposure to these compounds. Throughout this period, legislation was developed to strengthen the authority of regulatory agencies to control exposure to hazardous substances. This new legislation (including the Toxic Substances Control Act) greatly increased the need of regulatory agencies to know more about the toxicity of environmental agents.

Federal agencies began to intensify testing efforts. It soon became apparent that the Nation's testing capacity would benefit from better coordination and program integration. In 1978 the National Toxicology Program (NTP) was established for the purpose of coordinating and strengthening the Department's activities related to the testing of chemicals of public health concern.

The NTP, which was granted permanent status by the Secretary, DHHS, in 1981, has evolved into a major Federal resource for testing of chemicals and represents a leading effort in the world aimed at developing better, faster, and less expensive methods for determining which chemicals may be hazardous.

Dr. Wyngaarden suggested that these examples underscore the fact that while the generic mission of the NIH remains much the same, the NIH has demonstrated flexibility in its ability to extend mission boundaries in selected areas to meet special needs. This can be done without distorting its basic mission or jeopardizing the integrity of its traditional programs.

Dr. Wyngaarden then moved to the next item on the agenda and asked Dr. Joseph Rall to proceed with the discussion.

Historical Development and Future Prospects of Biotechnology

Dr. Joseph E. Rall
Deputy Director for Intramural Research

Dr. Rall indicated that this discussion would cover both the history and future of molecular biology. He spoke of the incredible changes that have taken place during the last 25 years in science and suggested that now would be an appropriate time to look back and see how it happened.

In reference to the NIH definition of biotechnology as expressed by Dr. Wyngaarden, he felt that there may be some research areas, such as protein folding, x-ray crystallography, and nuclear magnetic resonance, which are not adequately covered under this definition. He asked the speakers to consider the adequacy of the definition. He then introduced Dr. Zinder.

Dr. Norton Zinder
Professor, The Rockefeller University

Dr. Zinder felt the term "biotechnology" was overused and overextended. He did not favor seeing it expanded to include some of the areas mentioned by Dr. Rall. He felt that it should have been called "biological processing" but that "biotechnology" is what we must now live with.

He remarked that when one examines the sequence of discoveries within the fields of genetics, microbial genetics, and molecular genetics that led to biotechnology, one finds that microbial genetics stands at the crossroads. This is due to the fact that microbial genetics has reached a stage where it is possible to move genes, which is, of course, one of the major aspects of biotechnology.

Dr. Zinder traced the beginning of biotechnology, recalling that in 1944 it was shown in pneumococcus that DNA was probably the genetic material. In 1946 E. coli conjugation was described, and by 1948 a handful of people knew that if DNA was added to pneumococci it caused them to undergo type transformation. Dr. Zinder mentioned that the discovery of E. coli conjugation was fortuitous, as only one out of 30 strains have sexual conjugation. Most of the work he described took place in Dr. Lederberg's laboratory at the University of Wisconsin between 1948 and 1952.

Dr. Zinder recalled that his first task at Dr. Lederberg's laboratory was to identify auxotrophic mutants. At that time the techniques for doing such experiments were crude and he was having little success. Based on the realization that penicillin only killed growing cells, Dr. Lederberg suggested using this antibiotic as a way to select for biochemical mutants. Using this concept, a technique was developed which allowed for a much easier identification of mutant bacteria.

Dr. Zinder described how various mutants were selected for use as genetic markers. He recounted the results of early experiments using E. coli and Salmonella which led to the discovery of transduction and of bacteriophages. These discoveries were later used to map chromosomes, and the idea of creating recombinant DNA followed. Dr. Zinder recalled that most of the key nonchemical elements leading to recombinant DNA experiments were all discovered during those four years at Dr. Lederberg's laboratory.

Dr. Zinder concluded his presentation by describing some of the early experiments which demonstrated the role of restriction enzymes, another key element in performing recombinant DNA experiments. He reminded the participants that all of this took place before the chemistry of DNA was known. The work in microbial genetics laid the foundation for what was to follow.

Dr. Richards asked if history prior to 1948 influenced the work done in Dr. Lederberg's laboratory. Dr. Zinder felt that history did not play a productive role and, in fact, attempts to think in terms of classical genetics created problems regarding their work.

Dr. Rall asked about their source of funding during that time. Dr. Zinder said most of their funding came from the Wisconsin Alumni Research Foundation; however, they did have a number of other small grants from NIH, Camp Detrick, and the Rockefeller Foundation. He specifically noted that the work on phages was supported by the Polio Foundation and felt that this investment was extremely farsighted.

Dr. Pettinga noted that the work described by Dr. Zinder provides a good example of how industry, academia, and government worked together to produce a great deal of good science.

Dr. Maxine Singer
Chief, Laboratory of Biochemistry
National Cancer Institute

Dr. Singer stated that it is now possible to purify and clone essentially any gene or DNA segment from any organism. It is not even necessary to know what the gene product is. She referred to the term "backwards biochemistry" to describe the process involved in attempting to determine the function of a DNA segment after one has determined its structure. This sort of approach is being used to uncover the function of Z-DNA. Dr. Singer contrasted "backwards biochemistry" with "reverse genetics," where one takes a cloned DNA segment, alters its structure, and then determines the phenotypic consequences of that change.

She cautioned the audience to realize that our ability to do these things does not imply that they are always easy to do. Cloning certain types of sequences is still extremely difficult.

Dr. Singer suggested that one way to obtain a measure of how much has been cloned and sequenced is to examine how many sequences are currently held in the Los Alamos Laboratory databank; over one million base pairs are now logged in.

Dr. Singer, while confessing that it was difficult to select an area to discuss, given the extent of all the exciting work now being carried out, presented an overview of the regulation of gene expression and the question of how genomes got to be the way they are today. She noted that although research on gene regulation in bacteria provided a framework for questions dealing with eukaryotes, it did not prepare us for the sheer complexity of gene expression in eukaryotes. Dr. Singer reminded her audience that while her presentation would address what is known about the control of single genes, an understanding of development and differentiation requires that one examine interlocking networks and feedback loops that involve many genes.

Dr. Singer described the first kind of regulation of expression as the actual rearrangement of the genome. She cited three examples: (1) the assembly of immunoglobulin genes in mammalian B cells, (2) the variation in the mating type of yeast, and (3) altered surface antigens on trypanosomes. The examples suggest that this mechanism is ubiquitous.

The second process in which regulation can operate is in the initiation of transcription from a gene. She discussed several of the different mechanisms which can operate to turn a gene on or off and direct the point at which transcription will begin--including promoters, "up-stream DNA elements," and enhancers. She further described a negative counterpart to the enhancer which has been identified in yeast and is called a silencer. Dr. Singer also addressed the role of methylation of cytosine in cytosine:guanine dinucleotide (CG) sequences in regulating gene expression at the level of the initiation of transcription.

Dr. Singer then mentioned a number of additional factors such as regulation which can operate at the termination of transcription, and the role of splicing introns out of a eukaryote gene. The passage of an RNA molecule from the nucleus to the cytoplasm is another point at which regulation can occur. Parenthetically, she added that in considering regulation, one must not simply think of "off and on" signals but of relative rates of processing as well.

Dr. Singer expanded on the complexities involved, using promoters as an example. She discussed some of the differences between the action of RNA polymerases in eukaryotes and prokaryotes. She described at length what is currently known regarding the action of the three different polymerases which operate in all eukaryotes.

Dr. Singer described the work of investigators who have examined expression of genes in oocytes as contrasted with related genes that are expressed in the somatic tissues of the same species. Over the course of development, the oocyte genes are turned off. The mechanism is complex, involving protein factors and chromatin structure. All of these examples serve to illustrate the level of complexity that exists and our lack of understanding involving both the rate and the on/off nature of regulation.

Dr. Singer then moved to evolutionary considerations. To a large extent the history of contemporary genomes is written in their present structure. Accordingly, evolutionary biologists who follow molecular genetics have, in a sense, become archeologists.

It is striking to note that, in general, genomes have become larger with the passage of time. Recently, ideas have been proposed which could account for this increased size. One obvious factor is the multiplication of segments of DNA into tandem arrays. If a duplicated segment is a gene that is required, and if it makes a copy of itself in this way, then natural selection need only act on one of the copies to supply the required function. The second, third, or nth copy is free to diverge, either to become functionless or to evolve a new function and a new gene.

Copies made by known recombinational processes may also move somewhere else in the genome. An example of this is the relation between the alpha and beta globin genes.

Dr. Singer also described and provided an example of a phenomenon in which new genes are constructed from pieces of different genes joined in one place on the genome. She also described recent work suggesting that another way in which genomes increase in size is by reincorporating DNA copies of RNA molecules into the genome. Experiments indicate that a significant percentage of contemporary genomes, perhaps 3 to 10 percent, is due to this phenomenon.

Dr. Philip Leder
Professor and Chairman, Department of Genetics
Harvard Medical School

Dr. Leder began by saying that attempting to predict the future of biology is virtually impossible. This is due to the fact that we are dealing with biological systems delivered to us by the process of evolution.

He noted that there are two approaches employed when attempting to forecast the future of biology. The first approach examines clues found in contemporary biology and extrapolates from them. He cited as an example the work being done on gene regulation as described by Dr. Singer. One could predict that in the end this should lead to an understanding of certain inherited diseases which are fundamentally disorders of regulation.

The second type of futurism is based only on the faith that advances in fundamental biology will ultimately yield knowledge of great significance

and opportunity. Dr. Leder pointed out that there is no way of predicting what the ultimate fruits of such investigations will be. He believes that it is the responsibility of any civilized society to invest in the advancement of basic scientific knowledge, as that knowledge will ultimately be of relevance to all living organisms.

In considering some of the areas which offer opportunities for the advancement of knowledge and application, Dr. Leder pointed out that there are limits on our power to advance scientific knowledge.

In prefacing his remarks on the future applications of biotechnology, Dr. Leder purposely omitted the question of gene therapy, since the use of the new genetics to alter the genome of individuals has, for the present, limited application.

He believes that the new genetics will eventually resolve questions surrounding morphogenesis, the process by which organisms develop exactly the way they are. He stressed the important role of the study of primitive organisms in obtaining such new knowledge. While the function of important genes can be studied in men and mice, it can also be studied in organisms as simple as yeast. As a result of the relatively rapid generation time of simple organisms, some experiments which might take years in mammals can be done in days. While the use of such organisms is not new, Dr. Leder sees this approach playing a major role in the coming decades.

Dr. Leder believes that molecular genetics and other related techniques offer the only hope for a large group of intractable inherited diseases. He cautioned, however, that while the new techniques of molecular biology provide an approach to some of these difficult problems, there is no assurance that control of a disease process automatically follows a greater understanding of the disease.

He discussed some current diagnostic techniques and their benefits and speculated that molecular genetics could play a significant future role in the diagnosis and prognosis of cancer.

Dr. Leder stated that the production of therapeutic agents using biotechnology is limited only by our imagination and our knowledge of biologicals that may be of use to man. He cited anti-hemophilic globulin as an example of how recombinant DNA technology allows for the production of such an agent without fear of viral contamination.

Dr. Leder then turned to the issue of human gene therapy. While this technique has captured the popular imagination, there are only a small number of recessive disorders which are approachable by gene replacement therapy. While research in this area is vital and provides an interesting model system, it is still in a very early stage. The idea that we could offer human genetic therapy at the level of the germ line is ludicrous at this time. Perhaps some attainable goals stemming from the alteration of the structure of genes may be found in agriculture and animal husbandry.

Dr. Leder then described some recent work which illustrates both the opportunities and limitations of gene therapy. This work involved introducing a foreign gene into the genome of a mouse. He explained that once the mouse has taken up the gene it will be passed to its progeny. In describing the procedures involved, Dr. Leder noted that the technique would not be applicable in man. He provided a specific example in which a gene for growth hormone was introduced in a mouse and, once the gene was induced, the mouse grew two and a half times its normal size. Dr. Leder suggested there were obvious implications for animal husbandry inherent in this work.

The same sort of approach was used in experiments involving the introduction of an active oncogene into a control region that was supposedly expressed only in mouse breast tissue. In effect, a line of mice would be created in which all offspring would invariably develop breast cancer. This experiment was intended to gain some understanding of the development of malignancy. In addition, the experiment demonstrated one of the fundamental problems in gene therapy, which is, while you can put a gene in, you cannot control exactly where it will integrate nor how it will be expressed. Overcoming this problem in higher organisms will be a major challenge facing basic biologists and geneticists in the coming decade.

Returning to the example involving insertion of the oncogene, Dr. Leder described how this model provides opportunities for recognizing other oncogenes, for devising a test for mutagens, and for developing transformed cell lines. Discussing the model further, Dr. Leder explained that when one does introduce a foreign piece of DNA it will occasionally fall into an active gene. When this happens one creates an insertional mutation. While this phenomenon is a major problem in effecting gene therapy, it does provide an unusual insight as to how specific genes control development. This concluded Dr. Leder's presentation.

Discussion

Dr. Danforth asked Dr. Leder if he saw any differences in institutional support and structure necessary to carry on the type of research he described.

Dr. Leder responded by saying that during the beginning of his career only fundamental questions were addressable, with the use of simple organisms. Now complex organisms and complex questions are accessible to us. Young investigators today are inclined to pursue research involving higher organisms and complex questions rather than explore the genetics of simple organisms. This is in part due to the perception that NIH study sections will not support the type of fundamental genetics learned in simple organisms. Following a comment by Dr. Rall, Dr. Leder suggested that research using plants is also a problem, since it may not be considered health-related. He reiterated that expectations of funding and opportunities for career recognition play a major role in the types of research undertaken by young researchers.

Dr. Wyngaarden commented that much of the discouragement prevalent today rests on negative perceptions. While there is little chance NIH will experience the type of growth seen in the 1950's and 60's, the NIH budget

has, in fact, grown over the years, and the 1985 budget for NIH is the largest ever. There seems to be a mismatch between aspirations and reality. Despite the fact that NIH is now supporting twice the number of investigator-initiated awards as it did approximately 15 years ago, prior investments in research and training have tripled the applicant pool. While this has placed pressure on the NIH budget, one must not lose sight of the fact that the NIH budget has enjoyed greater stability than many other government-supported programs.

Dr. Wyngaarden went on to say that while some scientists believe that clinically related projects have a greater chance of securing funding, clinical scientists feel NIH favors basic science. He believes these perceptions are products of anxiety and, in most cases, would not bear up under the facts.

Dr. Richards brought up the question of training. Based on his experience, it seems as if most postdoctoral fellows are proposing research based on current knowledge and not suggesting anything really novel. While this approach can advance biotechnology, is it really advancing science?

Dr. Singer commented that research must go beyond molecular genetics and the associated techniques. One must also have an understanding of the underlying biology and chemistry. In her experience, most current postdoctoral fellows are adept at cloning and sequencing, but they lack knowledge of the chemistry behind the sequencing reactions. She was disturbed to learn that high school biology students are learning how to do recombinant DNA experiments rather than concentrating on the more fundamental aspects of biology and chemistry.

Dr. Zinder reinforced Dr. Singer's comments by saying that most students want to study extremely complex eukaryotic systems without spending enough time working with prokaryotes. He has also noted the feeling among students that funding opportunities are greater if your research is directly linked to problems involving human disease.

Dr. Newell asked if there is a problem with the educational process itself. Are students being encouraged to enter the laboratory too soon, without an adequate background in general biology?

Dr. Singer confessed that it was an extremely difficult question. Her own feeling is that young children should be taught natural history, as this gives one an appreciation of the diversity of biological systems. She acknowledged that this was simply her own bias and suggested that decisions on the content of educational curricula require careful analysis.

Dr. Zinder, referring to an educational project being conducted at the Cold Spring Harbor Laboratory, maintained that laboratory experiences seem to excite students. Permitting high school students to do recombinant DNA experiments is simply a way of capturing their interest. Only after this is done can you hope to expand their education into other areas of biology.

Dr. Singer remarked that the people they met in the laboratory made the difference. Dr. Zinder agreed that the enthusiasm of teachers is extremely important.

Dr. Wyngaarden returned to the issue of graduate students proposing "safe" versus creative projects. He wondered if this is a reflection of the system in which they operate. He questioned whether some of the changes proposed at the last DAC meeting regarding the lengthening of award periods and reduced emphasis on the mechanics of applications could influence this trend.

Dr. Richards believes it would be important, but cautioned against expecting too much change. He stated that creative research ideas are difficult to come by. His view is that the scientific community is unwilling to accept failure. When it comes to hard funding decisions, only what is known to be successful will be supported.

Dr. Wyngaarden then adjourned the meeting for lunch.

FIRST DAY
AFTERNOON SESSION

Federal Science Policy for Biotechnology

Dr. Wyngaarden convened the afternoon session, which was devoted to an examination of a national policy for biotechnology and the NIH's role within this context. He reviewed some of the current Federal activities addressing the questions of our national science policy and biotechnology, which include:

- the study being conducted by the House Committee on Science and Technology, chaired by Representative Fuqua, which is a long-range, comprehensive examination of broad science policy questions;
- the recent report of the President's Commission on Industrial Competitiveness, which, in part, called for the creation of a Cabinet-level department of science and technology;
- the White House Cabinet Council on Natural Resources and the Environment, which looked at the Federal regulations surrounding biotechnology to determine their adequacy and effect on the emerging industry; and
- the Public Health Service Ad Hoc Committee on Biotechnology, which identifies and attempts to resolve biotechnology issues that arise within the PHS.

Dr. Wyngaarden then introduced Dr. Bernadine Healy, who spoke on behalf of Dr. George Keyworth, Science Advisor to the President, and Director, Office of Science and Technology Policy.

Dr. Bernadine Healy
Deputy Director
Office of Science and Technology Policy

Dr. Healy stated that the future of our society is strongly influenced by leadership in science and technology. This is evidenced by a technological revolution unmatched in human history and spanning all areas of science. This revolution reflects the systematic broad support of basic science by the Federal Government. The influence of science on our society is also due to the fact that development and use of our scientific and technical knowledge has replaced traditional natural resources as a basis for economic growth. This has been noted both by scientists and industrial leaders.

These trends, while perceived by many with alarm, hold great promise. Dr. Healy recalled the words of David Packard, co-founder of one of the world's most innovative and competitive companies, when he stated that remaining competitive in changing times requires "talent, a zeal for winning,

and teamwork." Dr. Healy suggested that these should be watch words for both companies and nations wishing to capture the opportunities afforded by technological change.

She asked that we question how government can develop talent, stimulate the desire to win, and influence a national sense of teamwork. She believes that an adversarial relationship has developed among government, universities, and industry and that this represents a major obstacle in taking advantage of technological opportunities.

She described NIH as a leader in rapid technological change and the best biomedical research institution in the world. While there may be disagreement as to the operation of NIH, everyone supports the basic mission and shares in a desire to maintain the excellence which has characterized the agency.

NIH, by its very success, has created a knowledge base extending beyond the boundaries of medicine. There has been an increasing trend to merge the life and physical sciences. This trend has accelerated the pace of progress and success. We now face a challenge in attempting to apply the fruits of biomedical research into other areas, such as agriculture, computers, and the biotechnology industry. Dr. Healy posed the question of how NIH is going to face the challenge of fashioning non-medical tools for biology. What will be the relationship of NIH to other organizations that support biological research and what kinds of bridges will the biosciences build to other disciplines?

She described some of the problems facing the agricultural sciences, contrasting their levels of expertise and resources with biomedicine. Dr. Healy believes such problems call for a strengthening of the talent and knowledge bases, and she questions what role the NIH will play in this regard. She believes we must look towards NIH, since the real source of expertise resides there, despite the fact that research support will grow in other agencies. This, she suggested, indicates that NIH's traditional mission should be merged more closely with a broader national mission of ensuring our continued leadership in scientific research and training. The observation that NIH is becoming increasingly dependent upon advances in fields other than biology also suggests that NIH should play an active role in ensuring that our overall science and technology base remains preeminent.

Dr. Healy then emphasized that NIH should:

- continue a research program that ensures leading-edge health care;
- accept increasing responsibility in developing the knowledge and techniques necessary for biotechnology;
- ensure that it provides training for enough new talent to capture the fruits of the biological revolution;
- encourage the merging of the biological sciences with other fields of science; and

- recognize that its efforts have provided hope for a more secure, prosperous future.

Dr. Wyngaarden questioned what was meant by the suggestion to merge agencies in support of research and training. Dr. Healy responded that it was meant as a loose and broad goal, citing the Recombinant DNA Advisory Committee as an example.

Dr. Theodore Cooper
Vice Chairman of the Board
The Upjohn Company

Dr. Cooper began his presentation by reminding the participants that the current leadership of the U.S. in biotechnology is a result of science, not policy or micromanagement. He noted, however, that if one considers the various pieces of legislation which created the NIH and NSF to represent a formal Federal policy on research, then one could infer that such a policy accounts for the current status.

Dr. Cooper believes that a Federal science policy for biotechnology must consider four questions:

- What is our current policy?
- Is a change necessary?
- Are the underlying concerns for new policies centered on applications and products or on science?
- Is there a need for greater regulation and direction as opposed to the current general policy?

Dr. Cooper suggested that, in relation to the first question, there is a general consensus that the current approach of the U.S. has led it to world leadership in biotechnology. On the second question, while it is desirable to improve upon past success, Dr. Cooper believes that it may be unwise to tamper with approaches that work. Federal and industry roles are changing from their traditional ones, but that does not signify a loss of technological superiority.

Dr. Cooper believes that the public's main concern is the safety of biotechnology, which is a policy matter dealing with the endpoint of the process, not scientific exploration. From the standpoint of process safety, biotechnology is, and should continue to be, regulated.

Dr. Cooper maintains that the principal focus for future policy discussion should be on how the Federal Government can facilitate the growth of scientific activities related to the biotechnology enterprise. He stated that the best protection against losing our competitive edge is that of securing the best people and the best ideas and not by changing the focus of NIH

towards product development. Dr. Cooper doubts that a significant reorganization of NIH would increase its productivity and stated that we should "let NIH be NIH."

He agreed with Drs. Keyworth and Healy that there is a need for more training, and he favors tax and antitrust laws which would facilitate the development of biotechnology.

He reminded the participants that if we are concerned about losing our status as number one in this area, it is best to examine how we got to be number one in the first place. Dr. Cooper maintained that the growth and vitality of any endeavor is directly related to resources. While one may be concerned with councils, coordination, organizational structure, and regulations, ultimately budget is the critical element of the policy.

Dr. Cooper remarked that it is the private sector's role to develop commercially successful products from the pool of available knowledge. Moving NIH closer to development eventually translates into shrinking the pool of knowledge from which industry draws. From a scientific and historical point of view, this would be counterproductive. Shifting the NIH emphasis towards development could put off the next important breakthrough in the field of biotechnology.

As far as losing our competitive edge, Dr. Cooper remarked that, unlike the situation in some other countries, investments in developmental activities in the United States are made by the private sector. These private investments are currently expanding. The Federal policy in this country should continue to be on research and training.

Dr. Cooper stressed that attention to the infrastructure should be another major policy concern. The failure of companies to capitalize on new opportunities is often related to resources, not to know-how. Firms must also have enough resources to weather delays imposed by regulators--for example, waiting for the FDA to complete its review. Therefore, Federal policy should support the infrastructure and improve the regulatory process.

Dr. Cooper closed by saying that, while biotechnology is currently very high on our social agenda, it should not be the sole reason for making changes in NIH programs at the structural level.

Discussion

Dr. Wyngaarden summarized the contrasting nature of the last two presentations and asked Dr. Healy to comment on the suggestion that NIH loosen its mission boundaries.

Dr. Healy stressed that an important element in the success of NIH has been its central mission and that her remarks in no way implied that NIH's mission should be muted or lessened. There should be no motion away from basic research. The Federal Government should not be involved in developmental activities unless the private sector is unwilling or unable to do them.

Dr. Healy believes that the disease-oriented research mission of NIH should be interpreted broadly and that NIH should recognize that advances in fundamental biology can have applications in areas far beyond health and disease. What is really being suggested is not that resources be taken away from NIH but that NIH raise its consciousness of the fact that investment in the biological sciences is vital to a broader goal within our society.

Dr. Cooper asked Dr. Healy if her statements implied that investigators involved in plant biology should apply to NIH for support. Dr. Healy responded that if some good basic biological questions could be addressed through a plant system, it should be supported.

Stemming from a question posed by Dr. Cooper, Dr. Kirschstein stated that NIGMS does, in fact, support about \$2 to \$15 million of research involving plants, depending upon how such research is defined.

Dr. Cooper commented that the example cited by Dr. Kirschstein suggests that NIH does have the ability to support broad-based research. Attempts to influence selected areas of research support amount to micromanaging NIH programs. One of the great strengths of NIH has been its ability to support a broad base of general science even though it is largely organized around selected disease problems. It would seem as though the policy under discussion would merely facilitate what is already taking place. Dr. Cooper noted his support for a policy of broad-based research; however, he would be more encouraged if it were accompanied by additional resources.

Dr. Cooper, in response to a question by Dr. Gifford, stated that "generic research" should be the responsibility of private industry.

Dr. Wiesel asked about the status of the proposed Department of Science and Technology and how it relates to the earlier discussion. Dr. Healy reported that the recommendation for such an organization is still alive but is not likely to be implemented in the near future. She discussed the need for such a Department, saying that science and technology would benefit from a stronger voice in the upper levels of Government. She observed that an agency's place in the larger bureaucracy can influence its success. She cited NASA as an example of an agency which has done well, in part, due to the fact that it is a free-standing agency. The proposed Department could offer that same sort of autonomy to other science agencies.

Dr. Williams observed that there has been a linkage between government, universities, and industries in the support of research and the translation of knowledge into products. While the current issue is biotechnology, we must not lose sight of other ventures that are equally important.

Dr. Johnson recalled that the war on cancer was often compared to the space program. This analogy was flawed due to the fact that, unlike the space program, the knowledge and tools necessary to attack cancer were not available. He went on to say that exploiting biotechnology may be similar to the space program in that we do have a great deal of the knowledge and technology at hand. Therefore, the rate of progress in this area will be regulated by funding.

Dr. Newton observed that a great deal of interdisciplinary interaction currently takes place at NIH and asked Dr. Healy to elaborate on where NIH could be doing more in this area. Dr. Healy stated that she was not proposing to micromanage NIH. She reiterated that her remarks dealt with broad principles and expanded awareness on NIH's part. NIH must not view itself in an isolated fashion, only doing research directly related to disease. She recalled some of the comments from the morning session which indicated that young investigators were leaning towards disease-oriented research due to the belief that only such work has a chance of being funded. This she feels is a good example of the problem. Dr. Healy also agreed with Dr. Cooper's suggestion that NIH should not move into development activities. She noted, however, that NIH does have a responsibility to facilitate technology transfer.

Dr. Cooper closed this part of the discussion by suggesting that the real problem is a lack of communication. While there are examples of NIH taking advantage of new and broader opportunities, the perception persists that NIH operates in an "ivory tower." The problem, therefore, is to dispel this misconception, not to make changes in the management or structure of NIH.

Dr. Wyngaarden then asked Dr. Raub to introduce the next topic of the meeting.

NIH and the Support of Research Training in Biotechnology

Dr. William Raub, Session Chairman

Dr. Raub noted that the issue of research training had already surfaced earlier in the meeting. Before introducing Dr. Joklik, he stated that the following presentations would cover the university, industrial, and governmental points of view on this issue.

Dr. Wolfgang Joklik

Chairman, Department of Microbiology and Immunology
Duke University Medical Center

Dr. Joklik introduced his remarks as "the academic perspective on the impact that biotechnology has had in basic science departments." He pointed out that the 1980 Supreme Court ruling which allowed genetically engineered microorganisms to be patented had a profound effect on biology. Suddenly biologists could reap financial rewards for their creativity. Industry sought closer ties with academia. Scientists began to leave academia or devote part of their energy to applied industrial enterprises. Many bright and enterprising postdoctoral fellows in molecular genetics, molecular biology, immunology, and virology joined biotechnology firms. While this practice has occurred in such fields as engineering and computer science, it has never happened in biology before.

Dr. Joklik noted that while the establishment of professional relationships between industrial and academic scientists has had a major effect on only a

small number of universities, the movement of young scientists from universities into industry has had a profound effect. Soon there will be a major shortage of skilled teachers and academic research workers. This problem is exacerbated by the fact that biotechnology firms recruit only the very best young scientists.

Dr. Joklik maintained that it is difficult to predict how long this situation will last. Eventually, as biotechnology firms move away from fundamental research and into more intense developmental activities, some of these scientists may return to academia. At the moment, however, a very serious shortage of molecular geneticists, molecular biologists, immunologists, and virologists is developing. Even leading institutions are having difficulties filling positions in these areas.

Dr. Joklik described another factor accounting for this shortage. Today, few of the brightest undergraduates enter the field of academic biology. Although job opportunities and salaries have improved in this area, it has taken a long time for these facts to reach the undergraduates who are making career choices. Coupled with this is the observation that research training support has been depressed since the mid-1970's.

Dr. Joklik believes that in order to maintain our lead in biotechnology, improve our national economy, and assure a future adequate supply of scientists for industry and academia, NIH must substantially increase the amount of funds devoted to research training. These increases should be both at the predoctoral and postdoctoral levels in the areas of molecular genetics (at least a threefold increase) and molecular biology, virology, and immunology (at least a twofold increase). These increases should be in the form of training grants made to groups of investigators who have excellent track records in these areas. The emphasis should be on career training, not ad hoc technical training, with special attention paid to programs in interdisciplinary areas.

Dr. Joklik then highlighted many of the ways in which industry is now interacting with and dependent upon academia in the biotechnology area. He emphasized that when biotechnology firms begin to show sizable profits, they should assist in supporting research training. Dr. Joklik reviewed some of the benefits private firms would ultimately reap if this were done. He recognized that private contributions would never match NIH support but that they could amount to a sizable percentage of the total.

Dr. Raub then introduced Dr. Christoffersen.

Dr. Ralph Christoffersen
Executive Director of Biotechnology
The Upjohn Company

Dr. Christoffersen indicated that his remarks would follow on the theme presented by Dr. Joklik and that he would discuss both future personnel needs and how we might meet these needs.

Dr. Christoffersen characterized what typically happens after a major scientific breakthrough. If the breakthrough is to be properly utilized, a base of information and an attending infrastructure must be rapidly developed. To properly take advantage of the leads, training and the support of basic and applied science in this area will need to be substantially accelerated. The need for aggressive action is spurred by the fact that other countries are going to compete actively in this area.

Dr. Christoffersen then cited some specific estimates of need, cautioning that the numbers were intended to demonstrate trends and were not definitive. He presented evidence that there are roughly 25,000 people working in biotechnology and related areas. Given the fact that the rate of the overall U.S. labor force is expected to decline and that labor needs in biotechnology will expand rapidly, a shortage of trained personnel is a real possibility.

Using the pharmaceutical industry as an example, Dr. Christoffersen explained that in addition to the training needs of those not yet in the work force, a large percentage of the existing work force will need to be retrained in this new technology. He stated that a systematic assessment of these retraining needs has not been conducted and urged that such a study be initiated.

Using data from the Bureau of Labor Statistics, he concluded that by the year 1990 we may need approximately 37,000 individuals trained and retrained in areas which underlie biotechnology. He cautioned again that, although such estimates are rough, they make the point that there will be a growing need for personnel in these areas in the near future.

Dr. Christoffersen reviewed some results of a survey conducted by the National Science Foundation and made the following observations:

- Although the total number of graduates is increasing, by 1990 approximately one-third of those completing graduate degrees in science and engineering will be foreign students;
- Among graduate students, the percent receiving NIH training is decreasing;
- Compared with the total number of graduate students in science and engineering, the pool of U.S. full-time graduate students in the biological sciences is decreasing;
- More than 20 percent of the students in the biological sciences are foreign students, many of whom will return to their native countries upon completion of their education; and
- By 1990, there will be approximately 33,000 U.S. students with either B.S., M.S., or Ph.D. degrees in the biological sciences available for the U.S. employment pool.

Dr. Christoffersen commented that foreign students represent a drain on our existing training resources and bolster foreign competition. He indicated that the previous observations also support the contention that a substantial increase in training efforts is required.

Dr. Christoffersen stressed that training be broad and flexible rather than narrowly focused. This is necessary since we cannot predict which paths in the fields of biotechnology will present the greatest opportunities.

He recommended that:

- Personnel estimates should be revised to include the expansion of biotechnology and the need for retraining;
- Existing training programs should be expanded so that at least 4,500-5,000 persons per year are available for employment in U.S. biotechnology efforts; and
- Long-term support of basic research in the biological sciences should be substantially increased.

Dr. Christoffersen concluded that the aforementioned recommendations are vital to the full development of biotechnology and the maintenance of our competitive edge over other nations.

Dr. Raub thanked Dr. Christoffersen and next introduced Dr. Kingsbury.

Dr. David Kingsbury
Assistant Director for Biological, Behavioral, and Social Sciences
National Science Foundation

Dr. Kingsbury began by pointing out that the biological science supported by NSF is small when examined on national terms and that NSF effort deals with biology in a broad fashion.

A few years ago, after a review of the new developments in biology, NSF set as a priority support of fundamental plant molecular biology. Within this area there were personnel shortages, and several programs were developed to engage those problems. Dr. Kingsbury suggested that his experience with these programs provides some insight into the general field related to biotechnology.

Dr. Kingsbury described the selection criteria for the Special Postdoctoral Program in Plant Biology. A key element of the program was that the student would be cross-trained in two major areas related to plant science. Based on the large number of applications, it was apparent that there are a large number of excellent students who desire to receive training in a second field. Also, it was learned that a two-year tenure was not a sufficient period of time to really accomplish the goal of developing students with adequate knowledge in two fields. This was especially true when a student

was moving from molecular biology into plant biology. Dr. Kingsbury stated that NIH should be mindful of these facts as it considers its training programs.

He also mentioned an NSF program in environmental biology. It is another program set up to acknowledge a pressing need related to biotechnology.

Dr. Kingsbury stated that, based on a letter sent to all NSF grantees, it became apparent that a large percentage of academic investigators feel that retraining is a critical factor in their attempts to keep up with contemporary biology.

Concerning graduate training, he suggested that one way to increase the number of graduate students obtaining Federal support is to encourage their participation on research grants. While this approach should help, it will not alleviate future problems in personnel shortages.

Dr. Kingsbury believes we should be very concerned over the fact that a diminishing number of American citizens are interested in pursuing an advanced degree in science. He believes we should be doing more to highlight the exciting opportunities in science as a means of attracting students to science, even before they enter college.

Dr. Kingsbury concluded his presentation by discussing the rationale for the NSF Engineering Centers. These Centers make two contributions. One is to enhance the state of academic engineering in the U.S., and the other is to provide engineers with the kind of background that will make them valuable at the interface of biology and engineering.

Dr. Raub thanked Dr. Kingsbury and then summarized a presentation which was to have been delivered by Dr. Merritt, who could not attend the meeting.

Dr. Raub presented data which examined NIH research training in the area of biotechnology. In 1983, there were 1,500 predoctoral trainees, approximately 350 postdoctoral trainees, and more than 600 individual postdoctoral fellows receiving support in biotechnology or related areas. From 1979 to 1983, there has been an upward trend in both expenditures and the total number of individuals receiving training in this area.

Discussion

Dr. Pettinga asked if we should make a distinction between retraining researchers to use new technology rather than to become molecular biologists or biotechnology specialists. Dr. Kingsbury agreed that the principal need is to give researchers a full understanding of how to employ new research tools. Dr. Christoffersen commented that the initial training at the university should be as general as possible without sacrificing quality or technical ability. In the area of retraining, he stressed that a large number of researchers will need knowledge in new techniques and that the time necessary for such retraining will be substantial. Lengthy retraining periods will pose problems in taking people away from their current responsibilities to master new techniques.

Dr. Rall asked if there are significant problems in attempting to train researchers who are actively engaged with ongoing grants. Dr. Kingsbury responded, saying that the training periods are less than one year, that they relate to the grant itself, and that NSF believes the trade-off between training and moving forward with the project is reasonable.

Dr. Leopold asked Dr. Christoffersen if his data implied that no U.S. trainees received training abroad. Dr. Christoffersen responded that he did not intend to make such an assertion.

Dr. Newell asked for an explanation of a point raised at the last DAC meeting which indicated that the mean half-life of investigators with NIH grants is seven years. She wondered if the reasons for a short half-life relate to the current discussion. Dr. Raub felt that narrowness of training is not a principal factor but rather it is the intensity of the competition which accounts for the rapid turnover. Dr. Newell made the point that grantees should be able to adapt. Dr. Joklik agreed, adding that the amount of research funds affects the half-life of investigators.

Dr. Joklik indicated that training shortfalls in some areas may be severely exceeding the estimates presented by Dr. Christoffersen. He suggested there has been a significant drop in the number of trainees over the last ten years. Dr. Wyngaarden responded, saying that the total number of trainees has been relatively constant during the last nine years.

Dr. Richards suggested that sabbaticals for industrial research scientists would be a positive approach. He feels that there are indications that most valued senior industrial scientists leave the laboratory and move into administration. Dr. Christoffersen, in speaking only for his company, stated that this was not necessarily the case, since dual career ladders (in science and management) exist.

Dr. Wyngaarden, in the interest of time, asked that the discussion be suspended and asked Dr. David Rall to introduce the next session.

Biotechnology, Risk Assessment and Risk Management

Dr. David Rall

Director, National Institute of Environmental Health Sciences

Due to time constraints, Dr. Rall deleted his introduction and immediately introduced Commissioner Young.

Dr. Frank Young

Commissioner

Food and Drug Administration

Commissioner Young lauded NIH for its accomplishments and noted the leadership of both Drs. Fredrickson and Wyngaarden in regard to the Recombinant DNA Advisory Committee.

Dr. Young emphasized that, while biotechnology is at least 9,000 years old, the new biotechnology is infinitely more complex. Nevertheless, the two biotechnologies are fundamentally the same. Further, despite the complexity of the new biotechnology, we must not forget that our science will appear primitive from future perspectives.

Dr. Young cited some current risks of great concern in this area, including: (1) the continuous parenteral use of medications derived from microorganisms; (2) the possibility that, in fermentation biotechnology using cloned genes, mutations could arise in the coding sequence creating molecules with anomalous activity; (3) the release of genetically altered microorganisms into the environment; and (4) questions regarding human gene therapy.

Dr. Young noted that the Administration has formed an Interagency Working Group under the White House Cabinet Council on Natural Resources and the Environment to address these concerns. Some of its recommendations include:

- The assessment of risks should be based on the best scientific evidence;
- Science should be used to form a consensus within government, industry, and academe about the solutions to potential health hazards and associated risks of biotechnology; and
- The public must participate in decision-making regarding the risks and benefits of biotechnology.

Commissioner Young asserted that the FDA will be the key agency involved in the regulation of products produced by biotechnology research and that it currently has the necessary legal authority to protect public health adequately. He stressed that the FDA must assure the safety and effectiveness of those products it approves while not unduly hampering innovation. This dual responsibility has led to a case-by-case approach to regulation. The FDA does not believe that biotechnology has created a new paradigm, and consequently it does not plan to establish a new approval process.

Dr. Young discussed some of the key areas of regulation and highlighted some of the special concerns involved when biotechnology is used in the production of food, drugs, and vaccines. He made it clear that the FDA must have a strong core of scientific personnel in order to function effectively.

Commissioner Young described the case-by-case method which involves looking at the product, processes, and practices used in production and the standards used by the manufacturer before the product is released for human use. He mentioned that, unlike EPA and USDA, FDA usually does not have to deal with the deliberate release of organisms into the environment, due to the fact that it deals with medical compounds and diagnostic reagents.

Dr. Young concluded by saying that there are points to consider regarding human gene therapy and that he will be working closely with Dr. Wyngaarden on these issues.

Dr. Orville Bentley
Assistant Secretary for Science and Education
Department of Agriculture

Dr. Bentley stated that there has been a long history of introducing change into our plants, animals, and microbes that are used for food and fiber. Over the last 100 years, a State and Federal system has been established to assess the impact of introducing altered organisms and new technologies. This assessment system also involves interaction with user groups and universities. The current system should serve as a background for any future developments in the regulation of biotechnology as it applies to food and agriculture.

Dr. Bentley remarked that there is a great deal of excitement among agricultural scientists over the possibilities inherent in biotechnology. He cited environmental protection, pest control, and food processing as areas in which biotechnology will have a profound effect on the future of agriculture.

In the area of regulation, Dr. Bentley agrees with Commissioner Young that existing authorities are adequate to do the job and that the case-by-case approach is most effective.

Dr. Bentley explained that the Department of Agriculture is currently involved in two major relevant activities. One is the conduct of in-house research, and the second is the consideration of laws which deal with the registration and protection of plant varieties and other protective acts which are the responsibility of the USDA.

Dr. Bentley believes that the past several years of the RAC review process will serve as a useful guide as USDA reviews modified organisms before permitting their release into the environment. He indicated that USDA has a dual responsibility to avoid retarding entrepreneurial creativity while insuring the safety of such new products. He also views USDA as having an important responsibility in educating both the public and industry.

Dr. Bentley concluded his presentation by expressing his excitement over the future prospects for agriculture as the powerful new tools of biotechnology are brought to bear on old questions and difficult problems.

Discussion

Dr. David Rall thanked Dr. Bentley and suggested that regulating this new technology effectively without repressing it will be a major challenge for the regulatory agencies.

Dr. Wyngaarden, referring to an earlier conversation, asked Dr. Healy if she would care to comment on the issue of regulating biotechnology. Dr. Healy suggested that it is extremely important that various agencies with overlapping concerns and jurisdictions coordinate their efforts. She stressed the need to establish mechanisms which would insure ongoing communication on regulatory issues. She cited the NIH RAC as a model for the exchange of

scientific information. She believes that NIH will continue to play an important role in establishing and maintaining linkages between agencies.

Dr. Joseph Rall asked Dr. Bentley about the regulatory distinctions one can make between the cultivation and breeding of organisms when they occur as a result of natural or induced mutations versus the deliberate in vitro insertion of a specific gene.

Dr. Bentley responded that in the past the key regulatory activity had to do with the performance and efficacy of selected strains. It was not regulation in the same sense that we are discussing it now in regard to biotechnology. With the ability to insert a single gene or small group of genes, there is now heightened concern over the effect on the environment. He added that many of the methods used to evaluate new types of agricultural products prior to biotechnology can still be employed.

Dr. Anthony Robbins voiced a concern that people who have to regulate under existing law do not have an adequate science base. He believes that we should be doing more research from a regulatory point of view. An inadequate science base will either delay the development of new products or increase the chance that unreliable or unsafe products are released.

Dr. David Rall responded by saying that some products of biotechnology will really not be new; it is just that the method by which they are produced is different. In these cases regulation will not be a problem. In other cases, when one talks about new organisms, we do need more research. Hopefully, the case-by-case approach will allow us to identify those particular products which might potentially pose problems.

Dr. Bentley stated that in the case of some plants, such as corn and wheat, we already have a very extensive scientific knowledge base at hand.

Dr. Wyngaarden then adjourned the first day of the meeting.

SECOND DAY
MORNING SESSION

After welcoming participants to the second day of the meeting, Dr. Wyngaarden introduced Dr. Ruth Kirschstein, chairman of the session entitled:

Barriers to Industrial Progress:
Manpower, Financial, Regulatory, Information Access

Dr. Kirschstein noted that the morning's speakers were among those responsible for the commercialization of biotechnology. She then introduced the first speaker, Dr. Richard Nesbit.

Dr. Richard Nesbit
Vice President of Research and Development
Beckman Instruments

Dr. Nesbit began his presentation with an overview of the Federal budget, citing the relative importance of the DHHS budget in terms of impact on U.S. competitiveness in biotechnology.

He related his experience in trying to establish trade with the National Academy of China in 1981. Rather than buy the finished product, the Chinese were interested in learning how to run an instrument company themselves. They were surprised to learn that product excellence did not lead automatically to commercial success. For example, Beckman must compete with other companies for customers, employees, materials, and investors to succeed in the free market. Evidence of cultural differences emphasized the need for thoughtful communication.

Dr. Nesbit reiterated David Packard's remark, "What you need is talent, a zeal for winning and teamwork," adding "tools" as another need to this formula for industrial competitiveness. Referring to a claim made in the OTA's Report on Commercial Biotechnology that Japan is our leading competitor, Dr. Nesbit listed several recommendations for maintaining our edge in the international market. These included: fund new research and product development, provide real wages and health care, protect national security, and promote productivity.

Charts documenting Japan's favorable economic climate compared with the U.S.'s supported Dr. Nesbit's observations on our faltering competitive position. For example, it is much easier to raise capital in Japan to form a biotechnology firm. U.S. real wages have not increased over the last several years, and the return on capital investment in the U.S. is dropping. He made a strong case for changes in U.S. trade policy with regard to patents, export licensing, and exchange rates. Dr. Nesbit noted that proper protection for intellectual property is essential to attract investment capital and that the current patent system must be upgraded.

Dr. Nesbit expressed the importance of NIH support for intellectual leadership in boosting the economy. He stressed the need for adequate training in the new technologies, which must be accompanied by better equipment. He also felt that NIH can contribute to the promotion of a more realistic sense of health risks and a balanced perspective on environmental concerns. Standardized tests for health effects, he concluded, might serve to reduce interference with product development while maintaining safety.

Dr. Kirschstein introduced the next speaker, Mr. Robert Swanson.

Mr. Robert Swanson
Chief Executive Officer
Genentech, Incorporated, San Francisco

Mr. Swanson opened his remarks by stating that NIH has had a profound effect on the birth and development of the biotechnology industry and that the industry and NIH should work together to assure that the U.S. not only maintain its leadership in the basic sciences but also in its commercial development. Without NIH funding for basic research, biotechnology would not exist today. Mr. Swanson explained that the research of Genentech's co-founder, Herbert Boyer, was supported by NIH for 15 years and led to the critical discovery of restriction endonucleases. Further, Stanley Cohen also received NIH grants for his work on plasmids. When the two scientists got together, a new technology was born.

Mr. Swanson noted that basic research provides a broad array of valuable results and potential tools from which industry selects pieces that can be used in creating a new product. The manufacture and sale of those products creates new jobs and profits. A portion of the taxes from these salaries and profits goes to support basic research. Based on Genentech's success in achieving microbial expression of a human hormone, the technology advanced and resulted in the production of new medical, agricultural, and industrial products. One of more than 200 biotechnology companies, Genentech is responsible for the development of several medical products, including tissue plasminogen activator, interferons, tumor necrosis factors, a hepatitis vaccine, and human growth factor.

NIH has served as an effective intermediary, channeling the public investment in basic research and research training into knowledge that could be used in the development of these important products. Mr. Swanson described the small, new biotechnology firms as innovative and efficient at transferring technology from the university to industry. More jobs are arising in this sector than in large companies. For example, Genentech has provided 750 jobs, spent nearly \$150 million on research and development, and invested \$112 million in facilities for research and manufacturing.

Other countries, such as Japan, have capitalized on our investment in basic research. They are able to gain access to our technology. Consequently, Japan can focus on generic applied research, downstream processing, and manufacturing technologies. In this manner, production costs are reduced and fewer risks are taken. Japan also protects its home market and balance

of trade more stringently than the U.S. Mr. Swanson connected our declining position in the world market with a decrease in funds available for research. He provided an array of suggestions for ways in which the NIH could contribute to the excellence of science and its commercial development in the U.S., which included:

- Continue to conduct and fund basic research;
- Increase funding for bioprocess engineering;
- Encourage both the training of students and retraining of mid-career scientists;
- Establish training grants in biochemical engineering and fermentation technologies;
- Consider sending postdoctoral students abroad to learn about scale-up and downstream processing techniques;
- Continue to conduct clinical research and trials, particularly on new products;
- Serve as an expert witness and moderator in discussions of regulation and guidelines for the biotechnology industry and set standards for regulatory agencies such as FDA; and
- Foster collaboration and cooperation between industry, academia, and government.

According to Mr. Swanson, the biotechnology industry is in a precarious position. Enormous R&D investments have been made, but the industry has not yet reached the manufacturing and marketing levels at which it can be self-sustaining. By addressing the recommendations listed above, NIH can help the biotechnology industry maintain its international lead.

Next Dr. Kirschstein introduced Dr. Nanette Newell.

Dr. Nanette Newell
Director, Research Administration
Calgene, Incorporated

Dr. Newell spoke from the perspective of her earlier role as Project Director for the Office of Technology Assessment's publication "Commercial Biotechnology: An International Analysis." She identified two NIH mandates--research and training--and applauded the agency's efforts in those areas. She stated that it is essential that NIH continue in those roles because basic science will continue to influence and shape the biotechnology industry as it grows.

Citing the large numbers of foreign visiting scientists who come to work at NIH, particularly the Japanese, Dr. Newell urged that some reciprocity be

instituted by sending U.S. postdoctoral fellows abroad. Contrary to the "Not invented here" syndrome, there is much good science being conducted in other countries that could benefit the U.S. biotechnology industry.

Dr. Newell turned to a discussion of "generic applied" or "bridge" research, which she defined as that research which bridges the gap between the basic undirected research and very product-specific applied science. It is more structured than basic research but is also longer term and more risky than product-oriented research. Because of these last two points, and its broad application to the industry in general, Government support of generic applied research is appropriate, in Dr. Newell's opinion.

A slide taken from the OTA report showed that of the \$500 million spent by the Federal Government on biotechnology between 1982 and 1983, about 1 percent went toward generic applied research. In Japan and Western Europe, this ratio was closer to 50:50. In that report, Japan was rated as very high in potential competitiveness because of its expertise in fermentation technology, which at the time of the report's publication was thought to be the major route for commercial production of mammalian proteins. However, it is now known that mammalian cell culture systems must often be used to obtain a biologically active protein for pharmaceuticals.

Learning to culture mammalian cells on a large scale is an example of generic applied research. It is not a product-specific process, nor is it basic science, according to Dr. Newell. The United States has an opportunity to take the lead in developing this new technology. The Biotechnology Processing Center at MIT was cited as one example of ways in which this opportunity might be exploited. Jointly funded by NSF and NIH, the Center will concentrate on problems in the genetics and molecular biology of protein synthesis, processing, and secretion in mammalian cells and yeast.

Dr. Newell's final comment concerned the funding of generic applied research and access to the results. Small companies cannot afford to engage in this research extensively because of the amount of risk involved and the long lead time before its fruits become profitable. On the other hand, if the large companies conduct generic applied research, the information will probably be kept proprietary. This tends to keep small companies out, thus denying them the chance to exercise their innovative capability. Dr. Newell concluded by saying that in order to foster the entrepreneurial spirit of the small companies and help them to survive, the Federal Government should fund "bridge" research.

Discussion

Dr. Wyngaarden responded to Dr. Newell's remarks with information that NIH is engaged in discussions with the Industrial Research Institute (IRI) to explore ways in which NIH could work more closely with industry. One option under discussion is sending industry scientists to work in the NIH intramural program.

Expanding on this theme, Dr. Rall underscored the importance of NIH and IRI efforts to improve government/industry relations. He theorized that the advent of biotechnology disturbed the comfortable, defined relationship that once existed between academia, industry, and NIH. Only now are we beginning to develop more intimate interactions.

Dr. Wyngaarden asked how the work supported in the Small Business Innovation Research program (SBIR) differs from bridge research. Dr. Newell explained that the terms of the SBIR program are more suited for applied research than "bridge" research. Phase I grants for \$50,000 over six months do not cover a long-term, moderate risk project. For instance, Calgene executives have tried to devise SBIR projects but have found the terms too restrictive to support the initiation of new product research.

Mr. Swanson responded to Dr. Wyngaarden's question by stating that he felt that the SBIR program was a waste of money and that the Government ought not to be investing in product-related research that cannot attract outside investor financing. Rather, the Government role should be support of long-term, process-related research that is necessary to produce tomorrow's biotechnology products.

Dr. Korn remarked that the SBIR program illustrates the horrors of targeted, sequestered funding and that this meeting should not result in recommendations for further invasions into a budget that is already inadequate to support the basic science and training that everyone agrees ought to continue.

Dr. Guyton asked if there was any way that NIH could influence other parts of the Government to help overcome the advantage of lower production costs enjoyed by other countries. He observed that it seems we have made our market and our research open and available but have neglected to ensure some balance of trade. Dr. Nesbit replied that current tax policy does not favor industrial investment; however, he expects a return to equilibrium through increased production. He described a Japanese automated assembly line against which no small company would be able to compete unless it had the tools and capital to invest.

Mr. Swanson echoed Dr. Nesbit's sentiments and added that the beauty of automation technology is that it is capital-intensive rather than labor-intensive. Mr. Swanson proceeded to criticize the Government for tying industry's hands. For example, new pharmaceutical products cannot be exported prior to receipt of FDA approval. The large companies get around this by producing overseas, but this option is not available to smaller firms. Attempts to change the law are under way, according to Mr. Swanson.

Dr. Pettinga explained that the intent of this law was to protect third-world countries from unsafe, ineffective drugs. However, it has taken a long time for the country to realize that this prohibition affects small companies like Genentech far more than large companies such as Du Pont, Lilly, or Pfizer. He called it an example of how well-intentioned legislation sometimes goes awry.

Judging by remarks made by all three of the morning's speakers, Dr. Franzblau concluded that the NIH contribution to the government/academia/industry trilogy was adequate. He asked what industry was doing to aid efforts to usher in the next generation of biotechnology.

Mr. Swanson replied that he has testified before Congress that money should be added to the NIH budget to implement recommendations he made today regarding training and research. Dr. Franzblau stated that as small companies grow, they ought to take on added responsibility either by conducting their own R&D or, if that is too expensive, by offering some return on the public dollars invested in the R&D upon which the industry was built.

Dr. Nesbit disagreed with Dr. Franzblau's opinion that there is a one-way street between industry and academe. He noted, for example, that Beckman conducts its own research and collaborates and consults with university scientists. Furthermore, increased taxes paid by companies as they grow add to the two-way street that is already in place.

Reiterating earlier remarks, Mr. Swanson asserted that the free enterprise system creates a return on the public investment in research through taxes on industry's profit and on the wages of its employees. In addition, Genentech started with a collaboration between industry and academia when the company supported basic research done at Stanford, the City of Hope, and the University of California. Now, when Lilly sells insulin that was developed jointly at these institutions, they receive royalties. Genentech participates in a broad range of collaborative ventures with a large number of universities that hopefully will lead to similar returns to those institutions.

Dr. Farley, Fogarty International Center, spoke to the issue of research training that was raised earlier by Dr. Newell. First, the Fogarty Center supports about 50 U.S. senior scientists to go abroad each year to upgrade their knowledge. Second, the Fogarty Center administers a program supported by other governments that makes it possible for U.S. scientists to go to participating countries. These arrangements exist with France, Switzerland, Sweden, and West Germany, and negotiations are under way with Japan and Italy.

Dr. Danforth emphasized the importance of training in process development. He related the Washington University experience in setting up a center to train people in this area. The first difficulty was in locating faculty they had to recruit someone from abroad to lead the center. Second, funds are needed to compete with industry to retain faculty. Both these points indicate the need for additional funds to support a strong program.

Dr. Newton stated that all seem to agree that basic research and research training belong under the aegis of NIH. Support for intermediate research between basic and product development remains a problem. She suggested that industry follow a plan she observed in Canada in which small pharmaceutical companies successfully joined forces to support costly clinical trials.

After a brief recess, the discussion continued with Dr. Korn's request that the term "generic applied" research as it relates to biotechnology be further defined. He described how Stanford's Center for Integrated Systems funds generic applied research in electronics with joint contributions from both Government and industry. Participating companies gain access to a body of desired information and skills by sending their scientists to the Center. However, biotechnology seems to differ from electronics in that concern about proprietary questions precludes information sharing. Dr. Korn asked to what degree generic applied research is proprietary.

Dr. Pearson, an invited speaker, explained that having the ability to clone a gene for a desired protein and getting bacteria to express it does not mean that the product is ready to be marketed. There are still a number of technical difficulties that are not completely understood, such as degradation of the protein product prior to its completion and the formation of insoluble protein aggregates from which it is difficult to recover biological activity. These are problems that might be addressed in generic applied research.

In later discussion, Dr. Newell added to this definition of generic applied research with a quote taken from the OTA report. "Generic applied research is part of the continuum between the two poles of basic and applied." It might be characterized as follows:

- It is not committed to open-ended expansion of knowledge, like the typical university-based research, but is less specific than the typical industrial product- or process-development effort.
- It has more well-defined objectives than basic research but is longer term than typical applied research.
- It is high risk, in the sense that the stated objectives may fail and the resources committed may be lost.

Dr. Newell noted that Dr. Donald Kennedy has broken the research continuum into Phases I, II, and III. Phase II research takes place in various locations--from universities and institutions to nonprofit organizations such as SRI and Batelle. Its funding comes from a mix of public and private sources. The research is applied and focuses on processes. The environment is variable with respect to proprietary secrecy.

Dr. Kirschstein introduced the next speaker, Dr. Mark Pearson, formerly with the Basic Cancer Biology Program, Frederick Cancer Research Center.

Dr. Mark Pearson
 Director of Molecular Biology
 E. I. Du Pont De Nemours Company, Inc.

Dr. Pearson's remarks centered around the exchange of people between the industrial, academic, and Government sectors, the application of computer

technology for research in biology, and the importance of exclusive rights for industrial partners involved in cooperative biotechnology ventures.

The first barrier to innovation in biotechnology, in Dr. Pearson's view, involves innovative ideas. In the past, these ideas have come largely from research sponsored in the NIH Intramural Program and in the academic community. While there has been an increasing amount of innovative research generated in the small biotechnology companies, the larger firms have not fulfilled the expectations one might have of them in this area, although this is changing.

The next step is to transmit these innovative ideas to people who are able to implement them. Although publication in the open literature served this purpose in the past, Dr. Pearson noted that this method is becoming obsolete as scientists communicate their results much more quickly and freely than perhaps their corporate sponsors might wish. However, this speed is essential to our competitive position because it enables us to apply new technologies to product development rapidly.

Another critical factor in innovation is a sense of commitment in the industrial community. This sense is based on the expectation of a return on the investment, which focuses most heavily on skilled people. Still needed are both energy and good luck.

In order to provide some comparison between a small company such as Genentech and a large firm like Du Pont, Dr. Pearson listed some of the activities in which Du Pont is currently engaged. Biotechnology-related generic applied research programs are housed primarily in the Biomedical Product and Agricultural Chemical Product Departments. Basic research in the life sciences is conducted in the company's central R&D department in the areas of molecular biology, health sciences, plant sciences, and microbiology.

Roughly 25 percent of Du Pont's total R&D budget is committed to the life sciences--in biomedical products, agricultural chemicals, and basic research. Naturally, management assumes that over time there will be a return on this investment.

Dr. Pearson then turned to specific opportunities for NIH to promote innovation in biotechnology. First, he recommended greater freedom for NIH intramural scientists to enter into collaborations with industry. These might take the form of consultantships or actual time spent in industry laboratories, either on sabbatical or joint projects. This action would serve NIH in helping to retain senior, highly-regarded scientific staff who might otherwise be tempted to leave NIH for industry or academic positions. By the same token, industry scientists have spent time on sabbatical at NIH or as consultants to the Government on study sections and should be encouraged to continue to do so, according to Dr. Pearson.

Dr. Wyngaarden informed participants that this issue has been under discussion at NIH for more than a year, culminating in a document that is nearing

completion. Under certain circumstances, NIH scientists will be allowed to consult with industry if certain safeguards are met.

Dr. Pearson's next suggestion related to the increasingly important role that computer technology plays in biology. In the future, molecular modeling techniques and basic studies of protein structure may lead to the ability to design molecules with specific biological activities. The development of special-purpose, hard-wired computers and new software packages devoted to molecular modeling and analysis of protein dynamics has led to a new "cottage industry."

In addition, there is a growing community of computer scientists developing software that is useful in studying and predicting the behavior of proteins. A variety of data bases are growing from these studies that may one day be harnessed through artificial intelligence to design bioactive molecules. For these reasons, Dr. Pearson urged that these programs receive attention and support in order to enhance our competitiveness in the industrialized world.

In Dr. Pearson's opinion, NIH ought to promote joint ventures that are product and science driven, with the objective of accomplishing specific national goals. An example of one program that falls into this category is the AIDS research administered through NIH, particularly the National Cancer Institute and the National Institute of Allergy and Infectious Diseases. This program involves academic, Government, and industrial laboratories whose sizes range from small biotechnology companies to large ones such as Du Pont.

In closing, Dr. Pearson brought up the need to promote competition while trying to prevent redundant effort. He identified NIH as an appropriate body to help industry avoid such duplication.

Dr. Kirschstein noted that there are several SBIR grants involving the development of software and data base analyses and that NIH supports a number of data bases, particularly nucleic acid and amino acid sequence libraries.

She then introduced the next speaker, Dr. Irving Johnson, a member of the Recombinant DNA Advisory Committee.

Dr. Irving Johnson
Vice President
Lilly Research Laboratories
Eli Lilly Company

Dr. Johnson began by listing some of the accomplishments that have been achieved using the tools of biotechnology; for example, identification of oncogenes, development of a new generation of vaccines, and the detection of defective genes and viruses via nucleic acid probes. He attributed these successes to NIH's long history of support for basic research. Dr. Johnson

then turned to a discussion of national science policy and regulation of biotechnology as "barriers in industrial competitiveness."

According to Dr. Johnson, a comprehensive national science policy ought to include support for basic research and targeting for the areas of bio-processing, plant molecular biology, and biochemistry. Furthermore, he suggested improving intellectual property law, modifying import-export regulations, and regulating technology transfer rather than products.

The major portion of Dr. Johnson's remarks focused on the effects of regulation on industrial competitiveness. In his view, NIH responded quickly and effectively to the initial public concern regarding the safety of recombinant DNA research by establishing the RAC--a sound, responsible, and flexible scientific oversight system. This body, which provides for public participation, has been a major contributor to the fragile competitive lead which the U.S. enjoys in biotechnology, Dr. Johnson stated.

Next, he gave an overview of the state of biotechnology in other countries--how it is supported and regulated, and the kinds of products that are under development. He noted that the U.K.'s Department of Trade and Industry contains a biotechnology unit which seeks advice on the utilization of national resources and supports the efforts of private companies of all sizes.

In Japan, 14 companies have joined forces to create a consortium for biotechnology research. The Japanese government and this consortium encourage interest in investment by Japanese firms and assist in the transfer of this technology from biotechnology firms in the U.S. Citing data from the U.S. International Trade Commission, Dr. Johnson reported that Japanese firms hold 53 percent of U.S. patents granted in biotechnology-oriented processes for the production of amino acids, and Japan leads the world in enzyme technology. In the 1980's, funding of biotechnology research in Japan has risen by 20 percent per year, and the number of researchers, many of whom were trained in the U.S., has risen fourfold. The Japanese openly state that their plan is to catch up to the U.S. by scrapping older technology and improving upon new technology imported from the U.S.

Dr. Johnson feels that the U.S. regulatory scheme has a great influence on our ability to compete with Japan's organized effort. Slides describing the regulatory scheme proposed by the Office of Science and Technology Policy (OSTP) were used to illustrate Dr. Johnson's concerns. In the current system, all regulatory agencies are represented, albeit nonvoting. The plan under consideration establishes a Biotechnology Science Board, in an advisory capacity, to coordinate regulation. Although no provision was made for public participation in the original Federal Register notice, Dr. Healy has since suggested that this be rectified.

Dr. Johnson's principal criticism of the proposed regulatory scheme is that the products of biotechnology are examined under a different set of guidelines than those applied to classically manufactured products. This is particularly true of the review process outlined by the Environmental Protection Agency (EPA). He feels that the existing science base does not support the implied conclusion that genetically engineered organisms are more

dangerous than those occurring in nature. Furthermore, comparing biotechnology products to exotic alien species tends to feed the fears of the public that release of recombinant products into the environment will have untoward consequences. In Dr. Johnson's view, it is more appropriate to examine the product and its intended use rather than the process by which it was manufactured.

A member of the RAC, Dr. Johnson noted that this group is primarily concerned with the assessment of the scientific evidence supporting an application for permission to conduct recombinant DNA research. He agreed that there is a need for a single body to provide scientific oversight, but noted that the proposed Biotechnology Science Board has the potential to evolve into an inflexible, two-tiered system that will hamper industry efforts to market the products of biotechnology.

Dr. Johnson suggested that EPA rely on the expert advice of NIH's National Institute for Environmental Health Sciences (NIEHS). This agency investigates the effects of chemical, physical, and biological environmental agents on human health. Its charter is almost as broad as that of the EPA, but it has no regulatory authority.

To illustrate his concern for the deleterious effect of poor regulation, Dr. Johnson related the events surrounding an application by Drs. Lindow and Pannopolous of the University of California to permit the experimental release of a strain of *Pseudomonas*. This common strain has had a gene deleted that codes for an "ice nucleation" protein which promotes frost damage in the many cultivated crop plants it infects. The resulting so-called "ice-minus" strain also occurs in nature. Approval for this experiment was a lengthy drawn-out process, hampered by lawsuits and by EPA actions that repeated elements of the earlier RAC review. According to Dr. Johnson, expediting the approval of this "nonhazardous" experiment might have aided the Florida citrus industry.

Dr. Rall observed that under the current system, regulation is apparently imposed when the experiment is thoroughly understood, but not imposed if the techniques employed do not involve recombinant DNA or the results are actually less predictable. Dr. Johnson responded that he does not see a need to regulate experiments involving a single gene deletion. Instead, he feels that it would be appropriate to establish categories of research involving different organisms that would be exempt from requirements for extensive background information, based on the fact that the induced changes also occur naturally and often with less precision.

Examining the potential for a genetically engineered organism to move into an unusual ecological niche, Dr. Johnson stated that such chromosomal changes allowing this to occur are not unique to the province of recombinant DNA technology. New ecological concerns are constantly arising in a biologically dynamic world. The appropriate role of the RAC is to provide recommendations bearing on the applications of recombinant technology in previously unprecedented situations.

Dr. Johnson suggested, as an alternative to legislated regulation of research, the adherence to an existing set of principles that protects the rights of the public from danger brought on by the acts of scientists. There are questions every responsible scientist ought to ask himself before embarking on any project. This should lead to points to consider. A danger occurs when these points become subject to regulation, said the speaker. Freedom of scientific inquiry is a delicate entity to be protected at all costs within the constraints of common scientific practice. Furthermore, Dr. Johnson insisted, all scientists who work in biotechnology have a responsibility to keep the public informed as to what the technology is and what it can and cannot do.

The last speaker in this session was Dr. Brandon Price.

Dr. Brandon Price
Product Director, Cell Products
Damon Biotech

Dr. Price began by revising the accepted notion of a biotechnology industry as such, calling it instead a group of biologically based technologies and processes that permit the creation of new products for existing industries such as health care, agriculture, and food production. Damon Biotech, one of the smaller companies, was founded to commercialize a cell culture system called "ENCAPCEL" that offers the ability to grow mammalian cells to extremely high densities and to produce commercial quantities of biopharmaceuticals in pure form. The company specializes in the production of monoclonal antibodies for therapeutic and diagnostic applications. Dr. Price described several uses for monoclonal antibodies. One involves the replacement of polyclonal antibodies with the highly specific monoclonals in in vitro diagnostic tests. Still in clinical trials is a second application in which antibodies are tagged with a radioisotope that can be used in vivo--for example, to monitor heart damage following a heart attack, or in cancer management to watch tumor size as treatment proceeds or to scan for metastatic disease.

Monoclonal antibodies may also be used for cancer treatment either directly by attacking the cancer cells or indirectly by carrying a toxin or radioisotope to a specific target. The Scripps Clinic and Research Foundation is treating lung cancer patients with an antibody manufactured by Damon Biotech and conjugated to the drug methotrexate. Patient-specific antibodies are being made by Damon Biotech for use in the treatment of B-cell lymphoma.

Damon Biotech also supplies monoclonal antibodies for use in purification of recombinant DNA biologicals such as interferon or tissue plasminogen activator. All these applications of monoclonal antibodies can be expected to lead to a very large industry, with market sizes ranging from hundreds of millions to billions of dollars by the year 1990, according to Dr. Price. The U.S. leads the world in all aspects of monoclonal antibody activity, from the creation of hybridomas through the manufacture of products that are now either in clinical testing or are on the market.

The obstacles that slow the commercialization process are mostly technical. Examples of these technical issues include the definition and isolation of target antigens, the optimal methods for generating efficient antibody-producing cells, and the screening methods used to select those cells that will produce the antibody of choice for a particular application. The development of scale-up technology is yet another obstacle, the speaker explained.

Given these issues, how can NIH enhance and sustain U.S. leadership in the area of monoclonal antibodies and other biopharmaceuticals? asked Dr. Price. The first way is one that has been repeated by virtually all of the speakers. On behalf not only of Damon Biotech, but also of the two industrial associations--the Industrial Biotechnology Association and the Association of Biotechnology Companies--Dr. Price urged the support of basic research at ever increasing levels.

He made two further policy recommendations. First, NIH should establish subdivisions dedicated to biotechnology within each institute. The function of these would be to serve as a communications intermediary between biotechnology firms, academia, and NIH scientists, permitting freer access and improved information-sharing in all directions. In addition, the offices could compile data on work in progress at NIH and biotechnology companies in order to hasten the dissemination of information.

Second, Dr. Price suggested that NIH permit biotechnology firms to apply for grants that would be used to pay industry scientists while working on biotechnology-related projects in NIH laboratories. The industry scientist would work on problems of interest to NIH while gaining access to institute knowledge and other resources such as cell lines, tumor tissue, and laboratory animals. He sees this as a way to relieve manpower constraints suffered by NIH while providing companies with funds to conduct research, thus enabling them to keep capital in reserve for the support of more applied research such as development of scale-up technology.

Dr. Price closed by characterizing all of his recommendations as targeted toward the same objective--to ensure that U.S. biotechnology firms stay ahead of their competitors by helping them to determine the value of new substances and techniques so that they can invest their resources as rapidly and wisely as possible.

Discussion

Discussion turned to the question of NIH policy regarding patents on discoveries made by NIH employees. Dr. Nanette Newell had made the suggestion that NIH become more aggressive in its patent policy. Calgene is engaged in collaborative activities with universities, and when a product is developed, it is co-patented or, in some cases, the university holds the patent and the company gets licensing rights.

Dr. Wyngaarden asked Dr. Newell to expand on this recommendation. In his opinion, NIH has been aggressive in obtaining a large number of patents and is unique within the Government in this regard. She replied merely that

universities and NIH have not patented as many of the innovations in biotechnology as they might have. Dr. Johnson disagreed with Dr. Newell, claiming that NIH has been more active than some universities. Some of these patents have gone to small high-tech companies, including Genentech.

Dr. Swanson was also supportive of NIH efforts to promote transfer of discoveries to the public domain. He pointed out that in many cases, rights are left to the universities allowing them to profit from their discoveries. Dr. Swanson reminded listeners that the development process accounts for 90 percent of costs to industry and that exclusivity must be guaranteed as an incentive to make this investment.

Dr. Rall related how NIH learned the value of offering exclusive rights in order to induce a firm to undertake the marketing of a compound that had been developed by NIH intramural scientists. This task is now handled adequately by the National Technical Information Service.

Dr. Richards declared that the problem is on the university side. Faculty members have been remiss in recognizing the importance of their research and its commercial value, but that situation is changing.

Dr. Williams, returning to an earlier topic, noted that while there seems to be a consensus that generic applied research should receive funding, one must also keep the reality of a steady-state budget in mind. This issue can be dealt with either through a request for supplemental funds or by a re-ordering of the priorities for basic and applied research.

Dr. Wyngaarden's announcement that NIH was preparing to issue guidelines for NIH staff wishing to enter into agreements with industry stimulated the next question. Dr. Danforth asked Dr. Wyngaarden to describe the ground rules binding NIH staff who wish to serve as consultants. Dr. Wyngaarden remarked that the number of consultative ventures with a particular company and the fields in which such agreements take place must be examined for any appearance of conflict of interest. Dr. Wyngaarden described the extensive clearance procedure necessary to gain permission to conduct consultations. In addition, the guidelines will be reviewed periodically to be sure that compliance is maintained.

Dr. Richards introduced a new issue into the discussion--the importance of physical chemistry to developments in biotechnology. Today's graduate students are riding a fad based on recombinant DNA. They fail to remember that it is the gene product that bears industrial significance. He proposed a training emphasis on such unfashionable yet practical areas as protein folding and x-ray crystallography. Dr. Richards also sent a message to industry that help is needed in identifying manpower needs and communicating this to students early in their education rather than at the end of their Ph.D. training when they are job hunting. The rate of change in demand for particular kinds of students is so rapid that the usual market process is not taking hold in time to provide appropriate guidance.

The expressed need for x-ray crystallographers was amplified by Dr. Pettinga, who went on to identify additional manpower needs in the new biotechnology--for example, analytical chemists who can purify proteins. Also needed are chemical and computer engineers, not just molecular biologists.

Dr. Pearson agreed that there seems to be a lack of x-ray crystallographers. He offered the same solution for industry and academia that he posed for industry and Government, namely, joint ventures. He said that cooperative research programs are probably the most effective means both for generating products and transmitting the need for skills and talents to the people who can provide them, the students. Dr. Richards supported the mechanism of transferring personnel between industrial and academic laboratories.

Dr. Kirschstein reported that the number of predoctoral trainees that NIH has been able to support over the last 5-6 years has dropped 5-6 percent per year.

Dr. Nesbit queried the panel as to the best way to train scientists so that they can be flexible enough to adjust to rapidly changing technologies. Dr. Kirschstein replied that, at the predoctoral level, it is best to support broad, multidisciplinary programs. This allows for some fine tuning and greater focusing of interest at the postdoctoral level.

Dr. Danforth theorized that the pressure for specialization is created by students' anxiety about jobs. They want to learn the latest gimmicks, while faculty are concerned about teaching the basics and providing maximum flexibility for the future.

Dr. Christoffersen remarked that efforts at protein characterization, protein folding, spectroscopic characteristics, glycosylation, excretion through a membrane, and so forth, are questions to be answered through basic physical chemistry whether or not the product has commercial implications. In his view, this puts a different light on the notion that bioprocess engineering studies will form a different kind of activity for NIH. Any program, whether it is at the product-oriented or basic end of the research spectrum, must have a very strong component of basic physical chemistry.

Dr. Joklik was skeptical about the potential effect of NIH actions in this regard. Students are drawn to what is most topical, even when faculty are concerned with giving the widest possible training ranging from physical chemistry to biological systems. It is a sign of the times that students tend to concentrate on cloning without regard for what comes out at the other end.

At this point, Dr. Kirschstein turned the floor back to Dr. Wyngaarden, who adjourned the meeting for lunch.

SECOND DAY
AFTERNOON SESSION

NIH's Role in Fostering Biotechnology

Summarizing views expressed during previous sessions, Dr. Wyngaarden noted that the growth and development of the U.S. biotechnology industry will be conditioned by a variety of factors which have implications for innovation in general and relevance for this industry in particular. Some of the speakers' suggestions dealt with areas that are beyond the control of NIH, such as investment incentives and regulation, but important statements were made about emerging needs and priorities in areas where NIH might make a difference.

Dr. Wyngaarden noted that the most valuable contributions of NIH are in the support of basic research and training, so it would be useful to look at the nature of the NIH investment in those areas. In FY 1984 NIH provided approximately \$408 million in extramural support for research directly related to biotechnology and almost \$967 million of additional support for the broader science base underlying this field. In that same year, NIH also provided about \$29 million for training in areas directly related to biotechnology and \$49 million for training in the broader science base.

The NIH intramural laboratories serve as a unique resource in both research and training, and in FY 1984 NIH spent approximately \$200 million in these areas. This means that actual expenditures for biotechnology totaled \$1.64 billion, representing over one-third of the total NIH budget. In 1985 it is estimated that this figure will rise to \$1.8 billion, which is approaching 40 percent of a \$5.1 billion budget. These numbers characterize the heavy NIH commitment to biotechnology, which might be as large as we can justify, Dr. Wyngaarden observed.

Regarding comments that NIH might give greater emphasis to additional research areas, Dr. Wyngaarden noted that at one time our portfolio was somewhat broader, encompassing plant biochemistry and plant biology. It was decided that NIH could no longer support work on photosynthesis, and these projects were cut back. Later, that work was reinstituted but at a lower level of expenditure. The same is true in biophysics and organic chemistry, disciplines that are still actively funded but at smaller fractions of the total NIH investment.

These decisions were made in response to the growing competition for the research and training dollar, not because these areas were felt to be outside the NIH mission. When the perimeters of what could be funded were drawn more tightly, certain areas found themselves on the outside. The purpose of this meeting is to look at these boundaries again and perhaps to extend them. Dr. Wyngaarden concurred with Dr. Williams' statement that we must consider either reallocating existing resources or seeking new resources.

Dr. Wyngaarden observed that several questions have emerged that require further discussion. Among these questions are: What should be the role of NIH in the support of generic applied research with direct relevance to biotechnology? Are there special training needs that can be addressed by NIH? What other activities might be appropriately undertaken by NIH to further the goal of promoting biotechnology? Dr. Wyngaarden felt that these questions provided an opportunity for a rich discussion and that the afternoon's three outstanding speakers would help to focus thoughts on the solutions. With that, he introduced Dr. Donald Kennedy.

Dr. Donald Kennedy
President
Stanford University

Dr. Kennedy noted that on the central question concerning the appropriate role and mission of NIH, he sensed a convergence taking place at this meeting which he felt could be summarized as, "Stay as sweet as you are." In Dr. Kennedy's view, the question under debate has three parts: First, what is the problem? Second, what is needed to solve it? And third, a very important question, who ought to do it?

Dr. Kennedy referred to biotechnology as yet another example of the social process of innovation, which can be plotted as a trajectory bearing two points, an early point "B" for basic and a later point "P" representing product development. As one follows the upwardly sloping curve, the proportion of funding from private sources, or risk capital, increases relative to public support. Another important factor that changes is the character of the environment. Basic research is characterized by relatively open communications, restricted only by competitiveness with other laboratories. The industrial end, however, is fettered by understandable proprietary constraints. At that end, the work is objective-driven and management ensures that this is maintained.

The speaker then used this graph to grade the country on how well it conducts the processes at the two ends. The U.S. tends to rely more heavily on universities to perform basic research than do other countries. This is where more than two-thirds of the aggregated basic research is done. In addition, we are the only nation that has chosen the route of training the next generation of scientists in the same institutions that are doing the most fundamental research. Dr. Kennedy feels that this policy confers great strength on American science.

A number of recent public policy decisions have strengthened the entrepreneurial zone of activity. Among these are R&D tax credits that encourage the investment of venture capital in high-tech start-ups. In 1977-78, the total amount of venture capital available for these projects was less than \$100 million dollars. This year, it was over \$4.5 billion, according to Dr. Kennedy.

Hence, Dr. Kennedy was willing to give A's for work represented by the two ends of the graph. The problem is in the middle, getting institutions to

transfer technology from the fundamental to the product development domain. Shortening the diffusion time is a problem that has been documented by Comroe and Dripps as part of the President's Biomedical Research Panel. Dr. Kennedy named five additional difficulties:

1. The health of the buildings and facilities for the conduct of basic research,
2. Conflicts of commitment or interest on the part of faculty members involved in high technology ventures,
3. An undesirable degree of incentive for the separation of research from graduate training where there are frequent off-campus ventures,
4. The paucity of institutions for technology transfer, and
5. Regulatory and other uncertainties that face product developers with respect to how much return on investment they can reasonably anticipate.

This list does not allow much room for NIH to take effective action, Dr. Kennedy observed. Points 2 and 3 are university matters that must be negotiated with corporate sponsors and through their own regulatory devices. A number of experiments in this area are under way, but it is not known how many will succeed. As to point 5, Dr. Kennedy suggested trading some regulatory rigidity for more control over marketed products. Perhaps NIH could provide some relief here in terms of improved methods for chronic toxicology testing, but this is not something one can program.

This analysis left only one area for NIH to work on, in Dr. Kennedy's analysis, and that is improving the health of the research infrastructure. This program has been starving for 17 years, since the demise of the Health Research Facilities Act. This is not solely NIH's responsibility, but NIH can remind other mission agencies that the health of fundamental science is just as important to their domains as it is in health.

Dr. Kennedy closed with a few remarks on staying with what one is good at. Based on his experience in the Office of Science and Technology Policy under President Ford, Dr. Kennedy expressed the opinion that agricultural research suffers from not having obtained enough support for basic sciences to produce capability and breadth of quality, as NIH has created in the health area. Instead, agriculture has been captured by institutions that look first at application and only second at the fundamental health of the science. Consequently, it has run out of useful fuel.

Dr. Kennedy closed with an object lesson. "In a world in which newspapers buy baseball teams, in which airlines can't wait to get into the hotel business and minnows regularly diversify by swallowing larger fish, I think somebody ought to stick to their business."

Dr. Wyngaarden introduced the next speaker, Dr. Ray Gifford.

Dr. Ray Gifford
Head, Department of Hypertension and Nephrology
Cleveland Clinic Foundation

Dr. Gifford explained that, although primarily engaged in the practice of medicine, he spoke from the perspective of the clinical investigator and the standpoint of the American Medical Association, where he is Chairman of the Council on Scientific Affairs.

Dr. Gifford's involvement with biotechnology is just beginning as the Cleveland Clinic expands its research division in cellular and molecular biology. He described three principles developed under a new AMA initiative that involves industry, labor, Government, and many professional societies.

- It should be the role of government to fund basic research as well as some applied research.
- It is the role of industry to fund targeted research leading to product development, as well as some basic research.
- Federal funding of the research effort should be adequate to provide stability to the research enterprise.

Speaking as a member of the DAC, Dr. Gifford agreed that NIH is responsible for the basic research that has given the U.S. a preeminent position in biotechnology in the world. He viewed this as a proper role, one that should be continued and expanded, but not at the expense of other more traditional types of research. This means that ultimately incremental funds will be needed to adequately support both ongoing research in other areas and the burgeoning research effort in biotechnology.

Dr. Gifford was concerned that we may lose the competitive advantage we now enjoy to the Japanese, who have made biotechnology a high priority. Referring to the OTA report, Dr. Gifford noted that although the U.S. leads its competitors in support for basic research in biotechnology, we lag behind Japan, Germany, and the U.K. in support for generic applied research.

He asserted that this bridge research is essential for translating basic research findings into marketable products. He disagreed with Dr. Cooper's assigning industry the responsibility for this research, commenting that unless there are more scientists trained in bioprocess engineering, we will fall behind the Japanese.

Dr. Gifford expressed the wish that every member of Congress had been present for the discussions of the past two days, and that they had the OTA report on their required reading lists.

He asserted that thoughts on nurturing biotechnology acquire urgency with its potential for improving pharmaceuticals, vaccines, and diagnostic agents that will aid the physician in providing better medical care and for improving the environment and the world food supply.

Donning his DAC member hat, Dr. Gifford closed with the following recommendations:

- The NIH should seek incremental funding sufficient to maintain its current competitive advantage in basic research and in the training of scientists in biotechnology and bioprocess engineering, without jeopardizing the funding of other types of research and training.
- There should be a structured and established forum to facilitate an ongoing dialogue between NIH, NSF, FDA, OSTP, academia, and industry to discuss the issues pertinent to enhancing the U.S. position in biotechnology and removing the barriers that restrict its growth. Issues to be discussed in this forum include responsibility for supporting generic applied research and manpower needs in biotechnology.
- Scientists should be permitted to move between NIH and industry.
- There should be sharing of data bases.
- Consideration should be given to establishing subdivisions within Institutes for biotechnology, a novel idea introduced by Dr. Price which obviously has problems but is worthy of discussion.

Dr. Gifford again emphasized the urgency of this issue, both for economic and humanitarian reasons.

Dr. Wyngaarden introduced the last speaker, Dr. Donald Fredrickson.

Dr. Donald Fredrickson
President
Howard Hughes Medical Institute

Dr. Fredrickson commented on several aspects of the relationship between biotechnology and NIH. The first was that NIH has responded admirably to a need to alter its cultural view of industry. In retrospect, the fears of a liaison between Government and industry have turned out to be terribly exaggerated. Dr. Fredrickson noted that in matters of equity, in consulting (short of excessive involvement in management by professors), and in scientific freedom, there has been real progress and no terrible disasters in these newly formed relationships since they began a few years ago. Indeed, the enlightenment of industry has been remarkable to behold, he declared. Academic freedom has been preserved and industrial research has become more competitive. The NIH has also experienced a change in attitude as evidenced by its allowing employees to do consulting. However, the ability of NIH to supply all the needs of this relationship is limited. For example, problems of patents and equity with regard to government employees have yet to be faced.

Dr. Fredrickson then turned to an earlier suggestion that industry provide support for guest workers to conduct research in the NIH intramural program. Several issues surrounding Federal personnel policy in the national laboratories were discussed in meetings of the White House Science Council, which

David Packard chaired and of which Dr. Fredrickson is a member. For example, salary scales at NIH are not the same as those in national laboratories run by university consortia, making staff retention difficult for the NIH intramural program. The organization of the intramural program represents a continuing challenge for NIH, according to its former Director, because it is much more threatened than the extramural program.

Dr. Fredrickson then discussed the Howard Hughes Medical Institute (HHMI), noting the Institute's history of support for biotechnology in its early days, as well as the air of anticipation regarding its future role. The HHMI faces many of the same problems experienced by the NIH intramural program, such as employees entering into consulting and equity agreements and the assignment of intellectual property rights. Hughes often assigns patent rights to affiliated laboratories and allows them to impose their own royalty schemes.

At this time, HHMI contributes the equivalent of one-eighth of the NIH budget to the development of new biomedical research. This does not mean, however, that Hughes constitutes another NIH, said the speaker. As a creature of Congress, NIH is subject to the interests and concerns of its constituents. This ties the agency to a categorical focus under which it operates quite well. It should not be altered except to improve upon the established mechanism. However, this limits the ability of NIH to integrate activities within institutions or to better use resources to build bridges or create opportunities that are not being filled by the larger federal role. This is where Hughes can fit in. One way is to supply the bricks and mortar to replace obsolete laboratories, providing structure and aggregation to the Nation's institutions.

Specific projects contemplated by Hughes executives include study of the human genome and a program in molecular biophysics. Dr. Fredrickson concurred with earlier speakers who lamented the dearth of scientists trained in x-ray crystallography and protein structure. However, he reminded participants that the purpose of universities is not only to produce new knowledge and new talent so that we can win the race in biotechnology, but to train scientists of breadth and laymen to understand science and technology.

Dr. Fredrickson concluded by stating that Hughes is interested in making sure that all physicians are not biotechnologists, but that they understand what biotechnology is about and what promise it holds for their patients.

Conclusion

Dr. Wyngaarden noted a recurring theme heard throughout the two-day meeting-- that NIH ought to continue to do what it does best, but also to be open-minded and flexible as to where it can improve its performance. In addition, it would be well to examine the areas where our boundaries might be made more elastic in responding to concerns that surround the issue of industrial competitiveness.

Dr. Wyngaarden expressed appreciation that Dr. Healy was able to attend the entire meeting and would be able to carry back a sense of the discussion to Dr. Keyworth. Dr. Wyngaarden issued an invitation to Drs. Healy and Keyworth to continue this dialogue in the future.

Speaking for the NIH staff, Dr. Wyngaarden thanked the speakers, commentators, and members of the Advisory Committee for their participation in this very important conference. He concluded by observing that there was much to digest and discuss and that conclusions, plans, or new directions would be reported back to the Committee at its next meeting.

The meeting was adjourned at 2:33 p.m., on June 25, 1985.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

A handwritten signature in dark ink, appearing to read "Kurt Habel", with a stylized, cursive script.

Kurt Habel, Acting Executive Secretary,
Advisory Committee to the Director, NIH

A handwritten signature in dark ink, appearing to read "James B. Wyngaarden", in a cursive script.

James B. Wyngaarden, M.D., Chairman,
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APPENDIX

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